The effect of oestrogen and the menopause on the female lower urinary tract

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THE EFFECT OF OESTROGEN AND THE MENOPAUSE ON THE FEMALE LOWER URINARY TRACT

Thesis submitted to the University of London

for the Degree of Doctor of Medicine

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ADDENDA TO MD THESIS

THE EFFECT OF OESTROGEN AND THE MENOPAUSE ON THE FEMALE LOWER URINARY TRACT

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Chapter 3

Page 56 Table 3.3. Third line should read 'urethral sphincter incompetence'.

Page 57 Line 14. Should read 'producing a mechanical rise in urethral pressure'.

Chapter 9

Page 178 Line 3. Should read 'There was an almost identical number of premenopausal'.

Page 220 Line 11. Should read 'which appeared to account'.

Chapter 12

Page 243 Table 12.7. Cure rate for urge incontinence in the women given oestradiol should read 56%.

Page 256 Line 18. Should read 'was that 56%'.

Page 259 Line 6. Should read 'and this severely impairs the possible'.

ABSTRACT

Fluctuations in the level of oestrogen and progesterone during the menstrual cycle and in pregnancy are thought to influence female lower urinary tract function. Furthermore, the menopause and subsequent oestrogen deficiency have been implicated in the aetiology of a number of urogenital problems.

The aims of this thesis are to examine the influence of sex steroids on female lower urinary tract symptoms and the results of urodynamic investigation. In addition, as oestrogen deficiency has been associated with the development of the "urge syndrome", I propose to test the hypothesis that postmenopausal women with this condition will respond to treatment with oestradiol implants.

The first section provides a review of normal and abnormal bladder and urethral function in women, along with the investigations necessary to make an accurate diagnosis. The effects of oestrogen, the menstrual cycle and the menopause are then outlined. There follows a detailed examination of the evidence linking oestrogen deficiency with the development of lower urinary tract dysfunction and infection. As young women with eating disorders provided a model for the changes occurring postmenopausally, the pathophysiology of this condition is also given.

The second section describes the studies performed in this thesis and the results of each investigation are discussed. In the first study the effect of the menstrual cycle on urinary symptoms and videocystourethrography are determined. The second study assesses the prevalence of urinary symptoms in young oestrogen deficient women with eating disorders. The relationship between the menopause and bacteriuria in community dwelling women is analysed in the third study. Finally, in the fourth study a double blind, placebo controlled trial on the effects of 25mg oestradiol implants on the "urge syndrome" is reported.

In the third section the relevance of the study findings are discussed, final conclusions are made and suggestions given for future work.

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ABBREVIATIONS

AN	Anorexia Nervosa
BN	Bulimia Nervosa
BMI	Body Mass Index
CI	Confidence Interval
CMG	Cystometrogram
CRF	Case Report Form
COC	Combined Oral Contraceptive
D & C	Dilatation and Curettage
DI	Detrusor Instability
FSH	Follicle Stimulating Hormone
HRT	Hormone Replacement Therapy
ICS	International Continence Society
IQR	Inter Quartile Range
GSI	Genuine Stress Incontinence
LH	Luteinizing Hormone
LMP	Last Menstrual Period
MSU	Mid Stream Urine
OR	Odds Ratio
PFE	Pelvic Floor Exercises
PMC	Pontine Micturition Centre
PTR	Pressure Transmission Ratio
QoL	Quality of Life
SD	Standard Deviation
SERMs	Selective Estrogen Receptor Modulators
UPP	Urethral Pressure Profilometry
UTI	Urinary Tract Infection
VCU	Videocystourethrography

DECLARATION

The work contained in this thesis was carried out in the Urogynaecology Unit of King's College Hospital, London and the Eating Disorders unit of the Royal Bethlam Hospital, London between September 1996 and February 1999. All the studies were conducted by myself, but I am grateful for the assistance of my colleagues who helped in the recruitment of the patients and performed some of the urodynamic investigations. The studies had full local ethical committee approval and patients included all gave informed consent.

Andrew Hextall

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First and foremost, I would like to thank Professor Linda Cardozo, without whose help and constant encouragement this thesis would not have been possible. She gave me tremendous support and guidance during my time in her unit, as well as the opportunity to train in urogynaecology and meet other people with similar interests across the world. I both enjoyed and greatly benefited from the time spent working with her.

Life as a research fellow is one of teamwork and I am also very grateful to Kate Anders, Kelvin Boos, John Bidmead and Vik Khullar for their unfailing help and friendship. Their assistance in recruiting patients, and understanding when my work interrupted the smooth running of the urodynamics clinic, was invaluable. Sara Majid, registrar in psychiatry, kindly assisted in the study of women with eating disorders and I am also indebted to the radiographers at King's College Hospital who agreed to act as controls. I would also like to thank Richard Hooper, lecturer in medical statistics, for his advice and help in the statistical analysis of this work. Many of the illustrations in this thesis were produced in the photographic unit at King's College Hospital, and I am grateful to Yvonne Bartlett for her time and effort.

Finally, I would like to thank my wife Helen who made me endless cups of coffee and never once complained about the many hours I spent sitting at the computer writing up this MD thesis.

PUBLICATIONS AND PRESENTATIONS

The following work in this thesis has been published or presented to learned societies:

ORIGINAL ARTICLES

Hextall A, Cardozo L. Managing Postmenopausal Cystitis. Hospital Practice 1997; **June**: 191-198.

Hextall A, Cardozo L. Hormone replacement therapy for vaginal, urethral and vulval conditions. Journal of the British Menopause Society 1997; **June**: 22.

Cardozo L, Hextall A. The menopause and lower urinary tract dysfunction. Urogynaecologia International Journal 1997; **11(3)**: 103-107.

Boos K, Hextall A, Cardozo L, Toozs-Hobson P, Anders K, Treasure J. Lower urinary tract symptoms and their impact on women with anorexia nervosa British Journal of Obstetrics and Gynaecology 1999; **106(5)**: 501-504.

Hextall A. Oestrogen and lower urinary tract function. Maturitas 2000; **36(2)**: 83-92.

Hextall A, Cardozo L. Hormone replacement therapy. Oxford companion to the body 2000 (In Press).

Hextall A, Cardozo L. The role of oestrogen supplementation in lower urinary tract dysfunction. International Urogynaecology Journal 2000 (In Press).

BOOK CHAPTERS

Hextall A, Cardozo L. The effect of oestrogen deficiency on the bladder. In: J Studd, editor. The management of the menopause. Annual Review 1998. Lancashire: Parthenon, 1998: 39-47.

Hextall A, Cardozo L. Oestrogen deficiency and the bladder. In: Professor FR Perez-Lopez, editor. The menopause and third age of women. Spain: University of Zaragoza, 2000: 309-326.

Hextall A, Cardozo L. The effect of oestrogens and anti-oestrogens on the urogenital tract. In: Professor M Oettel and Dr E Schillinger, editors. Handbook of Experimental Pharmacology. Heidelberg: Springer-Verlag, 2000: 363-377.

Hextall A, Cardozo L. Effects during the lifecycle (menopause). In: Professor L Cardozo and Mr D Staskin, editors. Textbook of Female Urology and Urogynaecology. Isis Medica Media Limited (In Press).

Hextall A, Cardozo L. Oestrogens and the bladder. In: Mr M Marsh and Ms JE Compston, editors. HRT and the Menopause. Current therapy. London: Martin Dunitz Ltd, 2000 (In Press).

ORAL PRESENTATIONS AT INTERNATIONAL MEETINGS

Hormonal treatment of urinary incontinence (1997)
Overbridging the concept of experimental pharmacology to clinical practice in rational drug development. Focus on clinical urogenital pharmacology
Nordic symposium at the Grand Hotel, Stockholm, Sweden, 13th May.

Oestrogens and lower urinary tract function (1998)
Belgium menopause society symposium on urogenital atrophy
Hilton Hotel, Brussels, 21st March.

The role of hormones in the treatment of urinary incontinence (1998)
Workshop on Pharmacological treatment of Urinary Incontinence
International Continence Society, 28th Annual Meeting, Jerusalem, Israel, 14th September.

Hormonal influences on the female lower urinary tract: A prospective evaluation of the effects of the menstrual cycle on symptomatology and the results of urodynamic investigation (1999)
International Continence Society 29th Annual Meeting, Denver, 25th August.
Abstract published in: Neurourology and Urodynamics **18(4)**: 363-364.

A prospective controlled study of urinary symptoms in women with anorexia nervosa (1999)
International Continence Society 29th Annual Meeting, Denver, 25th August.
Abstract published in: Neurourology and Urodynamics **18(4)**: 398-399.

ORAL PRESENTATIONS AT MEETINGS IN THE UK

Urogenital problems after the menopause. What can be done? (1997)
Menopause study day. "A change for the better"
Treliske Hospital, Truro, Cornwall, 14th October.

Menopause and incontinence (1997)
RCN continence care forum annual conference and exhibition
The Cutlers' Hall, Sheffield, 12th November.

Urinary symptoms in women with severe anorexia nervosa (1999)
International Continence Society (UK Section) 6th Annual Meeting, Edinburgh, 9th April.

POSTER PRESENTATIONS

Hextall A, Hooper R, Cardozo L, Stringer C, Workman C (1998)
Does the menopause increase the risk of urinary tract infection?
British Menopause Society, Heriot Watt University, Edinburgh, 16-17th July.
Abstract published in: Journal of the British Menopause Society *4 (Supplement 1): 26.*

Hextall A, Hooper R, Cardozo L, Stringer C, Workman R (1998)
Urogenital ageing and the risk of urinary tract infection
International Urogynaecology Association, 23rd Annual Meeting, Buenos Aires, Argentina, 18-21 November.

SECTION ONE

CHAPTER 1

THE SETTING FOR THIS THESIS

1.1. INTRODUCTION

The work contained in this thesis was carried out in the urogynaecology department of King's College Hospital between September 1996 and February 1999.

Situated in Southeast London, King's College Hospital is a teaching centre which primarily serves the needs of Lambeth, Southwark and Lewisham Health Authority. The local population of just under ¾ million people is one of the most deprived in England with high levels of premature death, mental illness and infectious diseases including HIV and AIDS. The latest estimated age distribution of the subjects living in the local catchment area is shown in **Figure 1.1**. The hospital, which became a NHS Trust in April 1993, has 900 beds and employs 4000 staff with an annual budget of approximately £185 million. In 1998 over 460 000 patients were treated. The women's health directorate is one of the biggest departments and offers specialist services in urogynaecology, colposcopy, oncology, menopause, gynaecological ultrasound scanning, fertility and family planning.

1.2. DEPARTMENT OF UROGYNAECOLOGY

The department of urogynaecology was established in 1979 by Professor Linda Cardozo. Referrals are received from local general practitioners, district nurses and continence advisors, and consultant gynaecologists and urologists working at King's College Hospital and the surrounding district general hospitals. In addition, the unit works as a tertiary referral centre with difficult or complex cases frequently sent from throughout the United Kingdom and abroad. Professor Cardozo is at present the only consultant in the unit but she is assisted by a subspecialty trainee in urogynaecology, three research registrars (of which I was one), a urogynaecology nurse specialist and an auxiliary nurse. A research physiotherapist was appointed in 1997 and works in

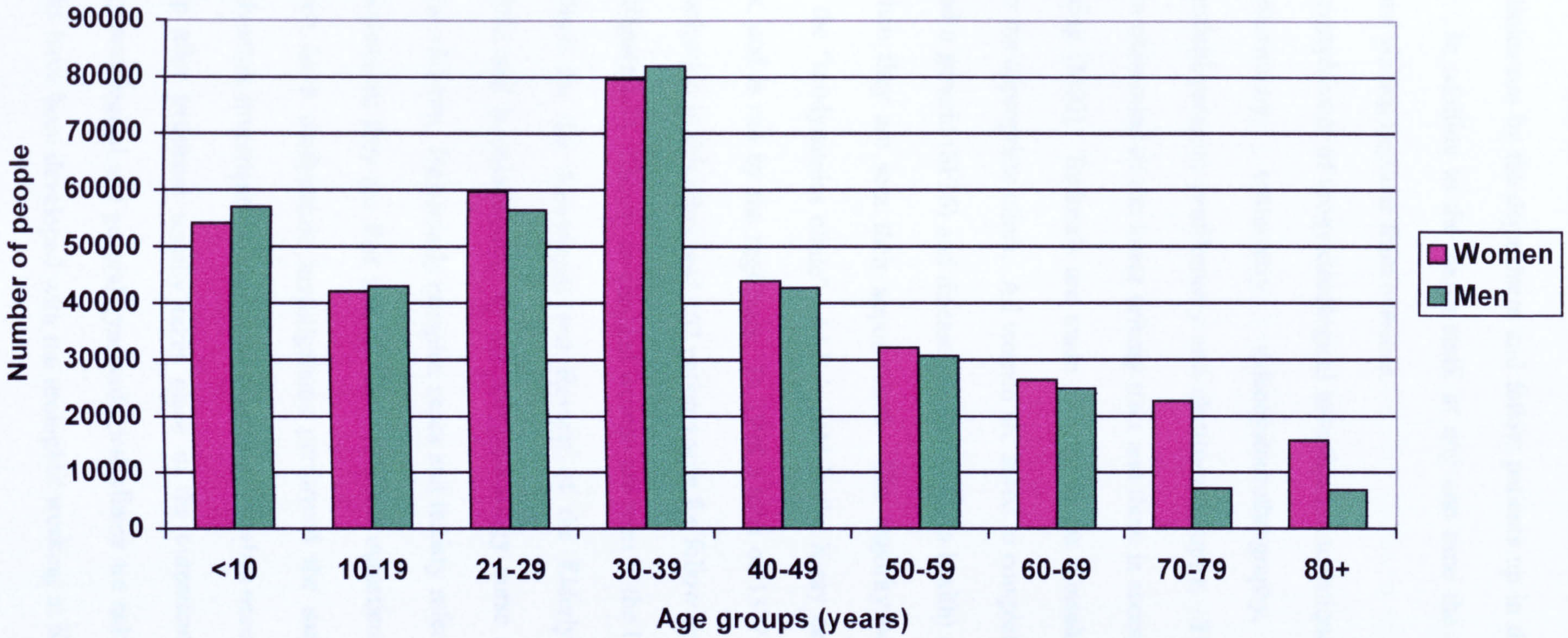


Figure 1.1.: Estimated population of men and women within the LSL Health Authority catchment area in 1998.

the department for 5 sessions each week. The district continence advisors also see women in the clinics run by the department and follow patients up in the community when necessary. In addition to the above staff, at any one time the department is usually host to one visiting registrar from overseas.

The full complement of urogynaecological investigation techniques is available including uroflowmetry, cystometry, videocystourethrography, ambulatory urodynamics, urethral pressure profilometry and electromyography. The unit has a special interest in ultrasound of the lower urinary tract and there is access to Magnetic Resonance Imaging (MRI). Referrals are made directly to the consultant who then allocates them to the appropriate clinic. All women are asked to complete a frequency volume chart, and a generic (SF36) and disease specific (King's health) quality of life questionnaire when they are sent their appointment. The majority of patients are initially seen in the "urodynamics clinic" which is held in the X-ray department five times each week, and is run by the registrars. In 1998 a total of 1377 women were referred for investigation in this clinic and 102 patients seen for follow up urodynamics after treatment (**Figure 1.2**). Elderly or disabled women are seen in the UCARE clinic (Urodynamic Clinic for the Assessment and Review of the Elderly) which was established in 1992 and is co-ordinated by the urogynaecology nurse specialist and district continence advisors. Particularly complex cases and tertiary referrals are given a "Job Lot" appointment; they are first seen in the consultant outpatient clinic in the morning and then have urodynamic investigations performed the same afternoon. Ambulatory urodynamic investigation is arranged subsequently when necessary.

Follow-up after treatment usually takes place in the outpatients department where both urogyanecological and general gynaecological clinics are held on a weekly basis. Close links have been developed with the urologists working at King's College

Hospital who attend fortnightly urodynamic review sessions at which complex cases are discussed. Other cases of interest are also considered at the pelvic surgeons meeting, which is held jointly with the urologists and colorectal surgeons every two months.

King's College Hospital with its urban and suburban catchment area and multi-racial population provided an ideal setting for the studies undertaken in this thesis. The large number of patients and great variety of lower urinary tract disorders seen in the department of urogynaecology provided me not only with a large study population, but also an excellent exposure to clinical urogynaecology.

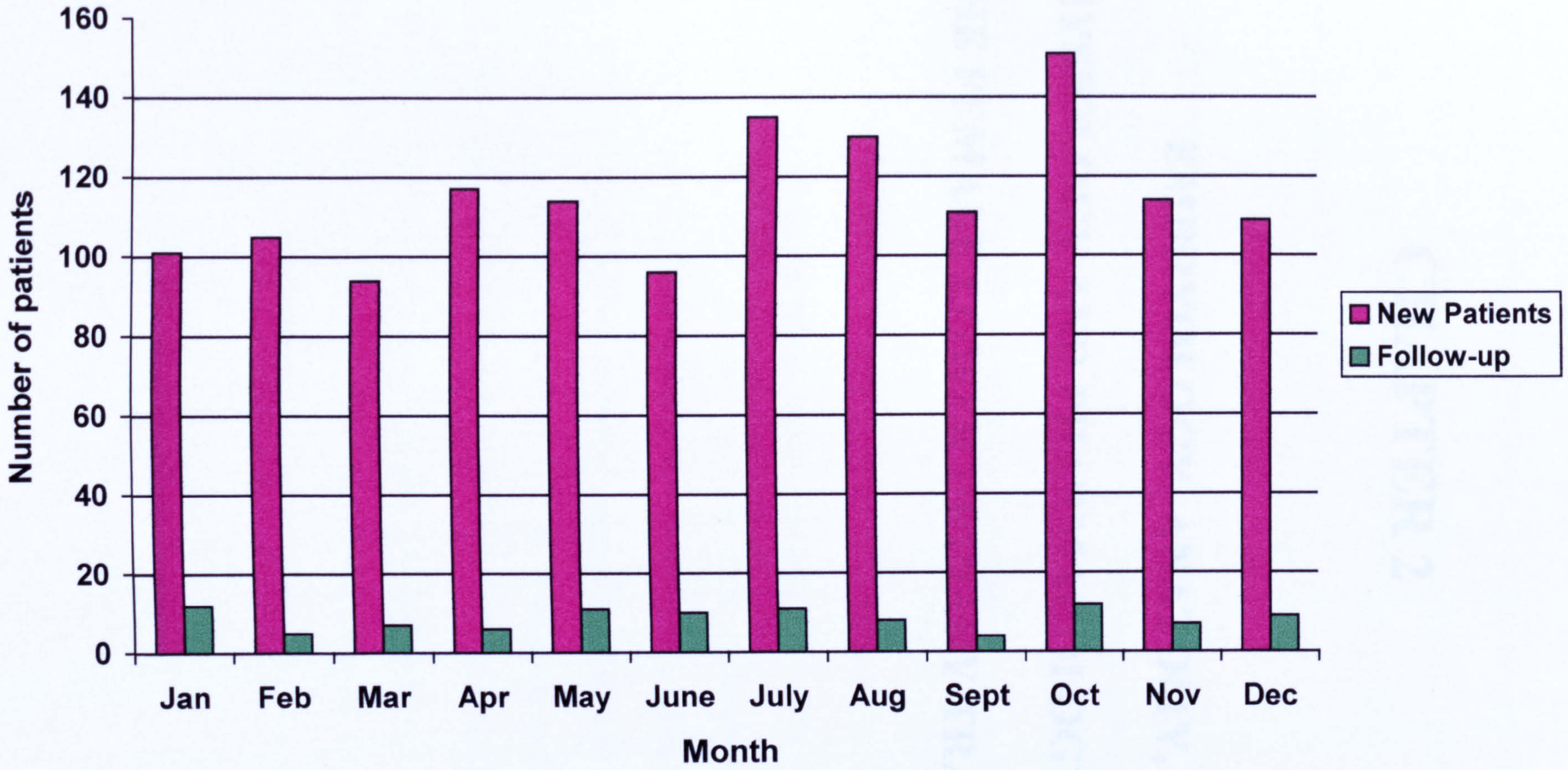


Figure 1.2.: Number of women undergoing urodynamic investigation in the Urogynaecology Unit at King's College Hospital in 1998.

CHAPTER 2

EMBRYOLOGY, ANATOMY, PHYSIOLOGY AND PHARMACOLOGY OF THE FEMALE LOWER URINARY TRACT

2.1. INTRODUCTION

The female lower urinary tract comprises the urinary bladder and urethra. The following chapter gives an outline of its embryology, anatomy, physiology and pharmacology. A detailed review of the hormonal influences on the bladder, urethra and continence mechanism is given in **Chapter six.**

2.2. EMBRYOLOGY

The female lower urinary and genital tracts have a common embryological origin, with both arising from the primitive urogenital sinus. The developing embryo is initially formed from three layers: endoderm, mesoderm and ectoderm. Approximately 15 days following fertilisation, cells differentiate from the primitive streak and migrate from the ectoderm and endoderm layers. This intermediate layer forms the intra-embryonic mesoderm, from which the pronephric, mesonephric and metanephric systems are derived, the latter two forming the definitive kidney and ureter. At the caudal end of the female embryo, the mesoderm fails to form and the ectoderm and endoderm persist as a bilaminar region forming the cloacal membrane. Mesoderm adjacent to the cloacal membrane produces bilateral elevations, the cloacal folds. During the fourth to seventh weeks of development a wedge of tissue known as the urorectal septum grows caudally between the allantois and hindgut **(Figure 2.1.)**, until it reaches the cloacal membrane, thereby separating the cloaca into an anterior urogenital sinus and posterior anorectum. The cloacal membrane is therefore divided into the urogenital membrane and the anal membrane.

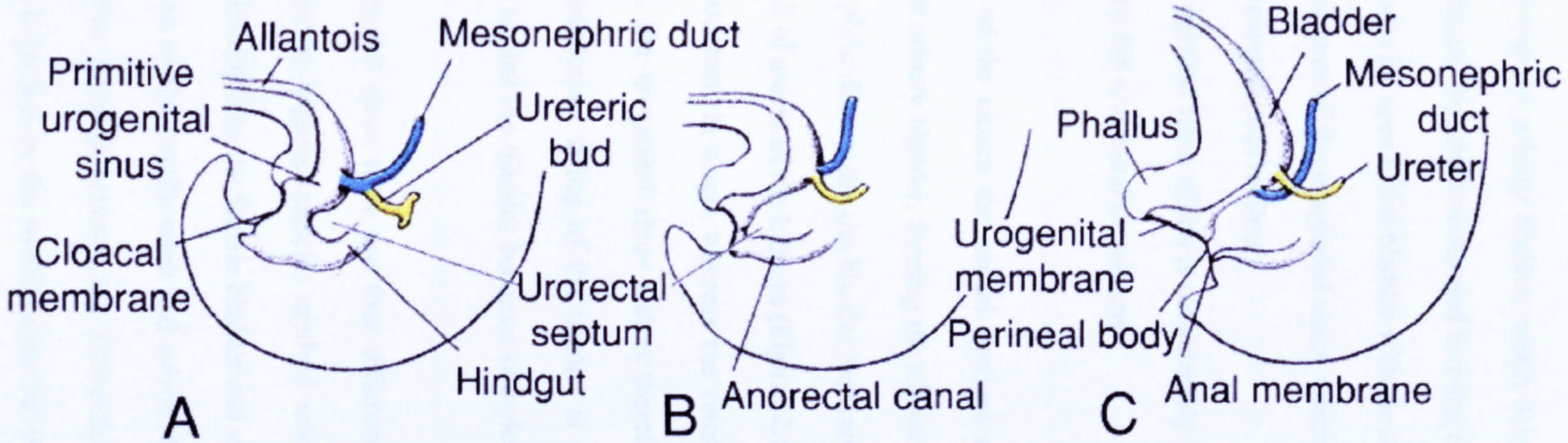


Figure 2.1. **Diagrammatic representation of the division of the cloaca into the urogenital sinus and anorectal canal, according to Sadler (1995). A: At the end of the 5th week. B: 7 weeks. C: 8 weeks.**

Three portions of the primitive urogenital sinus can be distinguished (Sadler 1995):

1. The upper part forms the urinary bladder, which is initially connected with the allantois. The allantois becomes obliterated forming the urachus, a thick fibrous cord which connects the apex of the bladder with the umbilicus.
2. The narrow pelvic part of the urogenital sinus, which in the male gives rise to the prostatic and membranous urethra.
3. The definitive urogenital sinus which is considerably flattened from side to side and is separated by the urogenital membrane.

During division of the cloaca the caudal portions of the mesonephric ducts become absorbed into the urinary bladder, forming the trigone. The ureters, initially out buddings of the mesonephric duct, enter the bladder separately (Gyllensten 1949) and move cranially as a result of ascent of the kidneys (**Figure 2.1.**). As a consequence, the trigonal mucosa is mesodermal in origin whereas the remainder of the bladder and urethra is derived from the urogenital sinus and is therefore endodermal in origin (Frazer 1935). The mesodermal lining of the trigone is subsequently replaced by endodermal epithelium, so that the bladder becomes completely lined with epithelium of endodermal origin.

Within the urogenital sinus there are four different embryological muscular promordia (detrusor muscle, trigonal muscle, urethral smooth muscle and urethral striated muscle) which develop into the female bladder and urethra (Droes 1974). The detrusor muscle is present by the twelfth week and surrounds the entire bladder. The three layers of the trigone develop between the sixteenth and twenty-fourth week. Urethral smooth muscle is present by the twelfth week but the urethral striated muscle does not develop until 16 weeks. Although the bladder and urethra appear to form a

continuous mass on gross inspection there are important differences from one region to another which can be explained by their different embryological origins.

At about 17-19 days after fertilisation, the mesodermal borders of the cloacal membrane thicken laterally to form the urethral folds and cranially to form the genital tubercle. In the female these structures continue to develop into the labia and clitoris. The urorectal septum becomes the perineal body in adult life.

2.3. ANATOMY

The bladder is mainly composed of detrusor smooth muscle fibres which can stretch to almost four times their resting length without increasing linear tension (Gosling et al 1999). In contrast to muscle in the gut distinct inner longitudinal and outer circular layers are not formed. Instead smooth muscle bundles act as inter-digitating slings (Bro-Rasmussen & Halborg Sorensen 1965) which functionally constrict as a single syncytial mass (Gosling & Dixon 1975). The bladder therefore is capable of storing increasing amounts of urine at low pressure for prolonged periods until emptying can be initiated at a convenient time. The bladder is covered by an adventitia and serosa over its dome, and is lined by a submucosa and transitional cell epithelium.

Within the lower aspect of the bladder is a triangular area known as the trigone, which is formed between the two ureteral orifices and the internal urinary meatus. At the base of the triangle is the interureteric ridge. The trigone contains a specialised group of smooth muscle fibres which arise from a separate embryological primordium. Above they are continuous with the smooth muscle of the ureters (Woodburne 1965) and continue below down into the urethra. The smooth muscle fibres of the trigone are smaller than those of the detrusor and have a greater density of surrounding connective

tissue. The mucosa in this region frequently undergoes squamous metaplasia and therefore differs from the transitional cell epithelium found in the rest of the bladder.

At the bladder neck the arrangement of the smooth muscle provides sphincteric closure of the urethra. Sympathetic denervation or damage to this area results in the bladder neck remaining open at rest (Stamey & Kaufman 1975). The highest intraluminal pressure is found in the proximal urethra where there is an inner longitudinal arrangement of muscle fibres, formed by a direct continuation of the fibres from the bladder, and a sleeve of outer circular muscle. In addition to this smooth muscle, striated muscle fibres surround 20-80% of the urethra forming the external rhabdosphincter. In its upper 2/3, the sphincter fibres lie in a primarily circular orientation. Distally they leave the urethra to encircle the vaginal wall as the urethrovaginal sphincter or extend along the inferior ramus above the urogenital diaphragm as the compressor urethrae. This muscle is composed largely of slow twitch muscle fibres which help to maintain its constant tone (Gosling et al 1981) and probably account for 1/3 of its resting closure pressure (Rud et al 1980). In addition, voluntary activation during times of raised intraabdominal pressure, compresses the urethra and increases urethral closure pressure.

The female adult urethra extends a distance of 3-4cm from the internal urethral meatus of the bladder to the external urethral meatus and has a mucosal lining of non-keratinizing squamous epithelium similar to that of the lower vagina (Carlile et al 1987). Throughout its length it is approximately 6mm in diameter. After an intramural portion 15% of its length, the urethra runs anterior-inferiorly (in the standing position), lying behind the symphysis pubis before traversing the urogenital diaphragm to reach the perineum. The distal 20% of the urethra is not involved in the continence mechanism (DeLancey 1986). Within the urethral wall is a well developed vascular

plexus (Berkow 1953) which has several types of specialised arteriovenous anastomosis allowing rapid changes in perfusion. Occlusion of arterial flow into these venous reservoirs influences urethral closure pressure and it is therefore thought that these vessels contribute to continence (Rud et al 1980). Interspersed within the muscle and submucosa of the urethra is a considerable quantity of both collagenous and elastin connective tissue.

The lower urinary tract is controlled by a complex interplay between the central and peripheral nervous systems and local regulatory factors (Andersson 1993). This is shown diagrammatically in **Figure 2.2.**. Contraction of the detrusor smooth muscle and relaxation of the outflow tract result from activation of *parasympathetic* neurones located in the sacral parasympathetic nucleus (SPN) at the level of S2-S4 (De Groat et al 1981). The axons pass through the pelvic nerve and synapse with postganglionic nerves in either the pelvic plexus, in ganglia on the surface of the bladder (vesical ganglia) or within the walls of the bladder and urethra (intramural ganglia) (Lincoln & Burnstock 1993). The *sympathetic* innervation of the bladder and urethra arises mainly from the thoraco-lumbar region T10-L2 of the spinal cord. The axons travel mainly in the hypogastric nerve but also pass through the paravertebral chain and enter the pelvic nerve. The predominant effects of the sympathetic innervation of the lower urinary tract are inhibition of the parasympathetic pathways at spinal and ganglion levels.

Bladder sensation is transmitted via several different nervous sources. Proprioception is relayed by myelinated Aδ fibres and long latency unmyelinated C fibres in parasympathetic afferents travelling in the pelvic nerve to sacral segments S2-4. The Aδ fibres respond to passive distension and active contraction, therefore conveying information about bladder filling (Janig & Morrison 1986). C-fibres have a

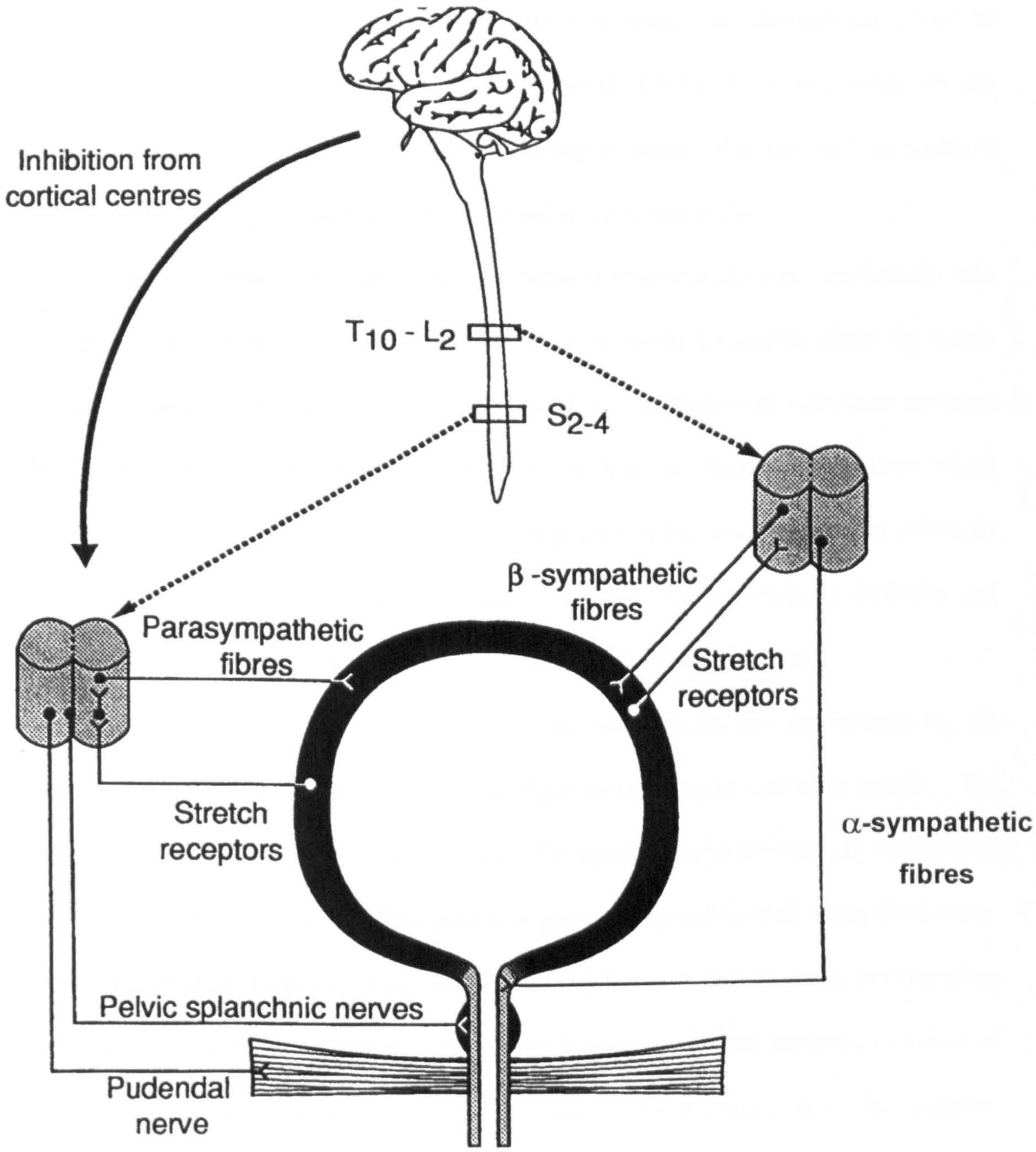


Figure 2.2.: Diagrammatic representation of the innervation of the lower urinary tract.

high mechanical threshold and respond mainly to chemical irritation of the bladder mucosa or cold (Habler et al 1990, Fall et al 1990). Somatosensory perception of fluid in the urethra and the external urethra sphincter is transferred through the pudendal nerve to sacral segments S2-S4 (Lincoln & Burnstock 1993). Abnormal sensation can be produced by a number of conditions including systemic illnesses such as diabetes mellitus and neurological disease of both the spinal cord and brain.

The continence mechanism can be separated anatomically and functionally into two units. The intrinsic continence mechanism consists of structures which lie within the vesical neck and are not specifically activated by contraction of voluntary muscles. The extrinsic continence mechanism usually refers to a group of structures which respond when an individual is instructed to stop their urine stream. This is primarily achieved by a constriction of the urethral lumen by the striated urogenital sphincter and an elevation of the bladder neck by contraction of the levator ani muscles.

The position and mobility of the bladder and urethra are determined by the fascia and muscles of the pelvic floor and their connection to the bony pelvis. The pelvic floor consists of several components. The upper layer is provided by endopelvic fascia which attach and suspend the pelvic organs to the pelvic side walls (DeLancey 1992). The part of the fascia which attaches to the uterus is known as the parametrium and composed of the cardinal and uterosacral ligaments. These structures consist of blood vessels, nerves and fibrous connective tissue. The structural layer that supports the bladder, also known as pubocervical fascia, is composed of the anterior vaginal wall and its attachment through the endopelvic fascia to the pelvic wall. Below the endopelvic fascia is the levator ani, which consists of the pubococcygeus and iliococcygeus muscles. The levator ani is attached at each end to the pubic bones and forms a U shaped sling of muscle passing behind the rectum in the midline. The

urethra, vagina and rectum pass through an opening in the levator ani known as the urogenital hiatus. Laterally, the iliococcygeus arises from a fibrous band on the pelvic sidewall known as the arcus tendinous levator ani. The levator ani forms a relatively horizontal sheet of muscle at the entrance to the pelvis on which the pelvic organs rest. In addition, via its attachment to the vagina the levator ani elevates and supports the urethra when there is an increase in intra-abdominal pressure. Close to the midline, the pubourethral ligaments also firmly attach the anterior aspect of the urethra to the posterior-inferior surface of the symphysis pubis. The interaction between the pelvic floor muscles and supportive ligaments is of crucial importance both to continence and the prevention of pelvic organ prolapse.

2.4. PHYSIOLOGY

The main role of the bladder is for the collection and expulsion of urine. At birth the bladder stores and discharges urine in a rhythmic manner which is independent of central cortical control. During the first five years of life this pattern comes under voluntary regulation, particularly during a period of adult supervision and biofeedback known as "toilet" or "potty" training. Similar methods are used in the treatment of incontinence **(Chapter three)**.

2.4.1. The storage phase of the bladder cycle.

The majority of the normal bladder cycle is spent storing urine at increasing volumes with a continuously low intravesical pressure which gradually results in central awareness. This is not purely a passive mechanism: the reflex contraction of the urethral rhabdosphincter is reinforced and there is reciprocal inhibition of bladder parasympathetic stimulation. This relaxation is in part enabled by a spinal reflex

pathway triggered by vesical afferent activity in the pelvic nerves, which initiates sympathetic firing from the lumbar region of the spinal cord (De Groat et al 1999).

Normal adult bladder function is characterised by quiescence of the parasympathetic efferent pathways and absence of involuntary bladder contractions during the filling phase. In addition, the pressure in the bladder remains low during filling because of the almost infinite *compliance* of the bladder until capacity is increased. This is largely achieved by the arrangement of detrusor muscle fibres, reflex inhibitory pathways and the absence of connective tissue restriction, particularly by collagen. Disturbance of any of these mechanisms can result in increases in intravesical pressure at lower bladder volumes than would normally be expected with the bladder then being described as hypertonic. Increases in intravesical pressure may lead to incontinence particularly if the urethral sphincter is compromised.

The bladder continues to fill with urine at a rate of 0.5-5 ml/minute, unless emptied, until it reaches its capacity (Hilton 1992). The *absolute* capacity of the bladder is determined by the vesicoelastic properties of the bladder, the physical limits of smooth muscle strength and the resistance of the outflow. However, in normal women the *absolute* capacity is rarely reached because the woman voids when the bladder has filled to its *functional* capacity. The *functional* capacity of the bladder is characteristically between 400-600ml (Cardozo et al 1993a) and depends upon bladder sensation, stability, compliance and voluntary voiding patterns.

2.4.2. The emptying phase of the bladder cycle

Micturition in women is incompletely understood but several key events are known to occur and these are co-ordinated by the pontine micturition centre (PMC) in the brainstem. The PMC receives information from afferent neurones in the bladder and

from the cerebral cortex and hypothalamus, and also controls the descending pathways of the micturition reflex. At a socially convenient time, following central initiation and then activation of the sacral parasympathetic nucleus, there is co-ordinated release of acetylcholine from the parasympathetic post-ganglionic nerve terminals in the bladder (De Groat et al 1993). There follows a depolarisation of smooth muscle cells with an inward flow of calcium. Actin/myosin activation leads to a sustained contraction of the detrusor smooth muscle fibres which provides the power for urinary evacuation. The urethra normally opens during this first phase of normal voiding, but it is unclear if this is an active or passive phenomenon secondary to an increase in intravesical pressure. In some women gravity alone may lead to expulsion of urine, with the patient simply having to relax the rhabdosphincter and pelvic floor. In others manual suprapubic pressure or voluntary straining may be necessary to enhance bladder emptying if there is diminished intrinsic detrusor function.

Urinary flow is determined using uroflowmetry with additional information gained by the simultaneous recording of intravesical and intra-abdominal pressures during pressure flow studies **(Chapter four)**. When normal, the flow appears as an abrupt rise in the flow rate followed by a gradual return to zero, with the residual volume of urine in the bladder typically less than 50ml (Cardozo et al 1993a). Some women retain a large residual volume of urine which has the effect of reducing the functional bladder capacity. For example, a woman who has an absolute bladder capacity of 600ml and post-micturition residual of 500ml may only have a functional capacity of 100ml.

2.5. PHARMACOLOGY

There are several regions of the lower urinary tract and micturition reflex pathways which are potential sites for drugs aimed for the control of bladder and urethral function. The main classes of therapeutic agents which may be useful for the treatment of lower urinary tract dysfunction are discussed below.

2.5.1. Central Targets

The supraspinal micturition reflex is under GABAergic tonic inhibitory control (De Groat et al 1993). GABA (γ-amino butyric acid) receptor agonists such as baclofen have been used to treat women with idiopathic detrusor instability (Taylor & Bates 1979) and detrusor hyperreflexia secondary to lesions of the spinal cord (Wein 1995). However, at present more effective agents are used as first line therapy.

The role of serotonin in the control of the lower urinary tract is complex and poorly understood but probably involves modulation of parasympathetic, sympathetic and somatic efferent pathways. Drugs which interfere with serotonin or serotonin receptors have not been systematically investigated or widely used for the treatment of urinary complaints (McMurray & Brading 1998).

The role of noradrenaline and dopamine in the central control of the lower urinary tract has also not been clearly determined. While stimulation or blockade of central receptors to these transmitters may have the potential to influence micturition and bladder disorders, the therapeutic benefits of such agents have not been established.

2.5.2. Peripheral targets

The preganglionic neurotransmission of the *parasympathetic* system is predominantly mediated by acetylcholine acting on nicotinic receptors, although transmission can be

modulated by adrenergic, muscarinic, purinergic and peptidergic presynaptic receptors (De Groat et al 1981). The postganglionic neurones in the pelvic nerve mediate the excitatory input to the human detrusor smooth muscle by releasing acetylcholine acting on muscarinic receptors which are found throughout the bladder. The preganglionic *sympathetic* transmission is similar to the *parasympathetic* system. Some preganglionic terminals synapse with the postganglionic cells in the paravertebral ganglia, while others synapse closer to the pelvic organs. Short postganglionic neurones innervate the target organs with their effect primarily mediated via the release of noradrenaline. The bladder neck and urethra have a dense distribution of alpha-adrenergic receptors and the bladder dome contains beta-adrenergic receptors.

Both normal bladder contractions and contractions in hyperactive bladders are predominantly mediated by acetylcholine acting on muscarinic receptors (Andersson 1993). Muscarinic receptor antagonists are currently the most important drugs for the treatment of bladder overactivity. Five muscarinic receptor subtypes (M1-M5) have been identified (Eglen et al 1996, Caulfield & Birdsall 1998). The human detrusor has a predominance of M3 receptors (Yamaguchi et al 1994, Wang et al 1995, Kondo et al 1995). Since excitatory neurotransmission is entirely cholinergic in nature (McMurray & Brading 1998), and the receptors present on bladder smooth muscle cell membranes responsible for mediating contractile activity are of the muscarinic subtype, antimuscarinics in low concentrations have been used to increase bladder capacity and block unstable contractions. All antimuscarinic preparations used in the treatment of urinary incontinence are reversible, competitive antagonists of acetylcholine. Non selective antimuscarinic agents such as oxybutynin are limited by their systemic anticholinergic side effects such as dry mouth, blurred vision and constipation.

Recently the selective antimuscarinic agent tolterodine has been introduced which has a much more favourable side effect profile. This is considered further in **Chapter three.**

Although adrenergic innervation in the human detrusor is sparse, a number of adrenoreceptor subtypes have been shown to exist, with a possible predominance of relaxation mediating β-adrenoreceptors (Andersson 1993). Application of β-adrenoreceptor agonists, such as Isoprenaline, to human detrusor muscle produces an inhibitory effect which causes smooth muscle relaxation. No differences have been shown in β-adrenoreceptor density between normal and hyperactive bladders (Restorick & Mundy 1989). However, it is possible that an atypical β-adrenoreceptor subtype is present in the bladder of some women, suggesting the possibility of developing new selective therapeutic agents. Unfortunately, the use of current β-adrenoreceptor agonists and antagonists for lower urinary tract disorders is limited by their systemic actions and side effects.

The normal human detrusor responds to noradrenaline by relaxing, probably via effects on both α and β-adrenoreceptors. However, the circularly orientated smooth muscle within the female urethra is under excitatory control by adrenergic fibres which act on smooth muscle cell membranes (Andersson 1993). Women with stress incontinence have been treated with α-adrenergic agents such as phenylpropanolamine, which may act by increasing intracellular calcium levels, causing a contraction of the urethral musculature and therefore an increase in urethral pressure.

Calcium channels are important local regulators of cell function. Of the six sub-classes of calcium channel currently known, only the L-type has been demonstrated within the smooth muscle of the bladder (Turner & Brading 1997). Upon membrane depolarisation, an influx of calcium ions into muscle cells can directly initiate a contraction (Ganitkevich & Isenberg 1995). Regulation of the intracellular calcium

concentration in the smooth muscle of the bladder is therefore a potential way to modulate a bladder contraction. However, very few clinical trials have investigated their use on lower urinary tract disorders. Although calcium channel antagonists have been shown to increase bladder capacity and reduce unstable contractions in women with detrusor overactivity (Rud et al 1979) they are very rarely used in clinical practice for this indication.

A number of different prostaglandins are synthesised within the bladder muscle (Andersson 1993) but they are not thought to be important mediators of bladder contraction during micturition. Although the exact mechanism of action of prostaglandins in detrusor muscle has not been studied extensively, it is possible that they contribute to its tone and spontaneous rhythmic activity (McMurray & Brading 1998). Prostaglandins may have an important physiological role by sensitisation of sensory nerves, and they have been implicated in the pathophysiology of a number of bladder disorders. Some women with cystitis may have an exaggerated prostanoid production leading to intense activation of sensory nerves (Maggi 1992). Unfortunately, side effects from prostaglandin synthesis inhibitors include nausea, headache and gastrointestinal symptoms which limit their use in clinical practice.

Oestrogen receptors have been isolated in the trigone of the bladder, urethra and muscles of the pelvic floor. The action of the sex hormones oestrogen and progesterone on the lower urinary tract, and the use of oestrogen replacement therapy to treat urinary complaints, is discussed in detail in **Chapter six.**

CHAPTER 3

LOWER URINARY TRACT DYSFUNCTION

3.1. INTRODUCTION

Treatment of female urinary symptoms including incontinence is perhaps the least glamorous but most rewarding division of obstetrics and gynaecology. Until the last 25 years few women admitted to suffering from incontinence and even fewer sought medical help. In a large study of patients seen after tertiary referral, Norton and colleagues (1988) found that 60% of subjects had delayed seeking treatment for more than one year from the time their symptoms became severe. Half of these patients said that this was because they were too embarrassed to discuss the problem with their doctor, and 17% said that they thought the problem was normal for their age. Unfortunately, many gynaecologists in the past have been reluctant to treat these "wet women" partly because incontinence is not a life threatening condition, but also because the causes were poorly understood. This often led to inappropriate and unsuccessful therapy.

Today more women are prepared to seek help but frequently on presentation they are embarrassed, depressed and often desperate (Wyman et al 1987). Normal daily activities which many women take for granted, such as going to a dance or playing with their children, may be severely affected with some patients becoming housebound for fear of leaking urine (Jameson 1983). Women with the symptoms of urgency and urge incontinence may be particularly severely affected because of the unpredictability and severity of their urinary leakage. This may lead to poor self-esteem with many women looking dishelved when they first present. The change in their appearance following treatment can be remarkable. Many come back for review wearing new clothes and make up with a new vigour for life.

The financial burden of incontinence in the United Kingdom is unknown but in 1986 the direct cost of continence pads and appliances was over £50 million with a

further £18 million spent on prescription items (Sanderson 1991). The costs of investigation and treatment are also substantial. Studies based on health care systems in the USA (Hu 1990) and Sweden (Ekelund et al 1993) estimate that urinary incontinence costs about 2% of national health care budgets or the equivalent to £1.4 billion pounds per year. There may also be the additional costs of residential care, as incontinence may also be an important factor when considering whether or not to institutionalise an elderly person (Sanford 1975, Ekelund et al 1987).

In this chapter I shall review the epidemiology, pathophysiology and treatment of the most common causes of urinary symptoms in adult women. The role of oestrogen, the menopause and oestrogen deficiency in the aetiology of urinary complaints is considered in detail in **Chapter six.**

3.2. LOWER URINARY TRACT SYMPTOMS

Women with urogenital dysfunction may present with a variety of lower urinary tract complaints. The urinary symptoms described in this thesis are defined as follows:

Frequency	Going to the toilet very often.
Nocturia	Getting up at night to pass urine.
Urgency	A strong and difficult to control desire to pass urine.
Urge incontinence	Urinary leakage associated with a strong desire to pass urine.
Stress incontinence	Urinary leakage with physical activity (e.g.) coughing, sneezing, running.

It is unusual for a woman to have only one complaint and common for a patient to have a variety of different problems. There is considerable overlap in the symptomatology associated with different conditions and therefore further investigation is almost always required to determine the underlying pathology. This is considered further in **Chapter four.**

3.3. EPIDEMIOLOGY

The International Continence Society (ICS) has defined urinary incontinence as "a condition where involuntary loss of urine is a social or hygienic problem and is objectively demonstrable" (Bates et al 1979). Estimates of prevalence vary according to the different populations studied, methods used for investigation and definitions used. The exact number of women with incontinence based on the ICS criteria is unknown.

Several large studies have evaluated the prevalence of urinary symptoms and urinary incontinence in community dwelling women in the last 20 years.

Thomas and colleagues (1980) surveyed the London boroughs and health districts of Brent and Harrow and asked for the number of notifications of people with incontinence each year. A postal questionnaire was also sent to all patients aged over 5 years on the lists of 12 general practitioners. Although the notified prevalence of incontinence in women aged less than 65 years was only 2.5% of the population, the results of the patient survey suggested that 25.1% of women had regular or occasional urinary leakage. Incontinence was reported less commonly by nulliparous than parous women, with those women having four or more babies most likely to report regular incontinence. Less than one third of patients with severe incontinence in this study were receiving medical help for their condition.

Jolleys (1988) surveyed 937 women attending a rural general practice and achieved an 89% response rate to her questionnaire. Of those women who took part in the study, 343 women (41%) complained of "inappropriate urinary leakage." The prevalence of urinary incontinence was again higher in parous women, but there was no recognisable association with the type of delivery.

O'Brien and associates (1991) studied 7300 adults randomly selected from one urban and one rural general practice in Somerset. Validated responses from a questionnaire showed that 4.4% of men and 16.4% of women had urinary incontinence, defined as "two or more leaks in any month." Only half of the people who were diagnosed as being incontinent took up the offer of treatment and it is possible that the diagnostic criteria used was too strict with many patients not having a social or hygienic problem as defined by the ICS definition of incontinence. It is clear from this and other reports (Wyman et al 1987, Norton 1990) that the severity of symptoms does not always

correlate with the psychosocial impact perceived by the individual sufferer. In addition, patients with frequency and urgency may be bothered as much by their symptoms as those with daily incontinence.

Several reports have suggested that the prevalence of incontinence increases with age. In an American study performed in the state of Michigan (Diokno et al 1986) trained interviewers visited the homes of 1955 senior citizens aged 60 or more. Any respondent who reported "losing urine of any volume with a minimum frequency of 6 days within the last 12 months" was considered to be incontinent. There was a significantly greater prevalence of incontinence in women compared to men (38% v 19%), with 9.0% of the incontinent female population complaining of urge incontinence, 27% stress incontinence and 56% mixed urinary leakage. The remaining patients with incontinence were unclassified. The frequency of voiding was significantly increased among subjects with incontinence compared to those who were asymptomatic ($P<0.001$). Of the women studied, 11% complained of difficulty emptying the bladder and 18% had problems with pain, burning or stinging during micturition. In an analysis of a MORI poll Brocklehurst (1993) also found that the prevalence of incontinence increased in each decade of life. However, only 12% of the incontinent women over the age of 60 in this study thought that their age was the cause of their problem.

A report providing the average prevalence of incontinence from all the available data has been produced by the Royal College of Physicians (1995). This is shown in **Table 3.1.**.

Population	Age (years)	% Incontinent
Women living at home	15-44	5-7
	45-64	8-15
	65 and over	10-20
Men living at home	15-64	3
	65 and over	7-10
Both sexes together in institutions		
• Residential homes		25
• Nursing homes		40
• Hospital (elderly and elderly mentally infirm)		50-70

Table 3.1.: Percentage of the population with urinary incontinence. Figures are based on an average of data from epidemiological studies (Royal College of Physicians 1995).

At present a very large Medical Research Council (MRC) funded prospective study is taking place in the University of Leicester which will hopefully provide a better understanding of the natural history incontinence and of other lower urinary tract symptoms.

3.4. AETIOLOGY OF LOWER URINARY TRACT SYMPTOMS

There are a number of different conditions which may cause urinary symptoms and incontinence in women (**Table 3.2.**). The two most common problems, genuine stress incontinence and detrusor instability, are considered below along with an overview of the main causes of irritative urinary symptoms. It is important that an accurate diagnosis is made before therapy is instituted because the treatment of each condition may be completely different. This is particularly the case when surgery is being contemplated, as the results may be irreversible.

• Genuine stress incontinence
• Detrusor instability
• Overflow incontinence
• Fistulae
• Urethral diverticulum
• Congenital anomalies (e.g.) ectopic ureter
• Functional (e.g.) immobility secondary to arthritis
• Temporary (e.g.) constipation, urinary tract infection

Table 3.2.: Causes of female urinary tract symptoms and incontinence.

3.4.1. Genuine stress incontinence

The symptom of stress incontinence may occur in women with a variety of different lower urinary tract pathologies. However, it is only after urodynamic investigation that genuine stress incontinence (GSI) may be diagnosed with accuracy. This condition is defined as "the involuntary loss of urine when the intravesical pressure exceeds the

maximum urethral closure pressure in the absence of detrusor activity" (Abrams et al 1990). While incontinence associated with coughing or exercise is the predominant symptom in women with GSI, patients may also complain of frequency, urgency and a variety of other problems.

The aetiology of GSI is complex and incompletely understood. A number of different pathological processes have been implicated (**Table 3.3.**) including intrinsic deficiency of the urethral sphincter, bladder neck hyper-mobility, reduced pressure transmission to the proximal urethra, changes in collagen and the development of a neuropathy. The role of the menopause and oestrogen deficiency in the development of GSI is considered in **Chapter six.**

• **Raised intra-abdominal pressure**
(e.g.) Pulmonary disease, constipation, pelvic masses
• **Urethral sphincter incontinence**
(e.g.) Damaged intrinsic sphincteric mechanism, hyper-mobility, denervation
• **Decreased or absent urethral pressure transmission**
• **Trauma**
(e.g.) Surgery, childbirth
• **Bladder overdistension**
(e.g.) infrequent voiding, neuropathic overflow incontinence
• **Congenital abnormalities**
(e.g.) short urethra
• **Collagen deficiency**
• **Oestrogen deficiency and the menopause**

Table 3.3.: Factors implicated in the aetiology of genuine stress incontinence.

3.4.1.1. Conservative management of genuine stress incontinence

Conservative (non-surgical) treatment of genuine stress incontinence should be considered in all women presenting with GSI. However, it is particularly useful for young women who have not completed their family and those unfit for surgery. Simple behavioural changes such as avoidance of precipitating factors and regular toileting to keep the bladder relatively empty can be useful first line measures. Women with incontinence should also be advised to limit their fluid intake to 1500ml per 24 hours.

The mainstay of conservative treatment for GSI is pelvic floor physiotherapy which was first introduced by the American gynaecologist Arnold Kegel (1948). Pelvic floor exercises (PFE) appear to work by a number of different mechanisms. Strength training may increase muscular volume and structural support to the bladder and urethra during rises in intra-abdominal pressure (Bo 1995a). During a pelvic floor muscle contraction the urethra may also be pressed against the posterior aspect of the symphysis pubis, producing a mechanical rise in urethra pressure (DeLancey 1988). Furthermore, as up to 30% of women with stress incontinence are unable to contract their pelvic floor correctly at presentation (Bo et al 1988), some patients may simply need to be re-taught the "knack" of squeezing the appropriate muscles at the correct time (Miller et al 1998). Cure rates varying as widely as 21-84% have been reported (Kegel 1948, Bernstein 1997, Bo et al 1999). Success appears to depend upon the type and severity of incontinence treated, the instruction and follow-up given, the compliance of the patient and the outcome measures used. However, it is clear that PFE's are more effective if patients are given a structured programme to follow, rather than simply being given verbal instruction and left to perform the treatment unsupervised at home (Henalla et al 1989, Bo et al 1990, Lagro-Janssen et al 1991a).

The success of PFE's may be further enhanced by the use of biofeedback (Burgio et al 1986). This technique allows patients to receive visual or audio feedback relating to contraction of their pelvic floor. The most commonly used device in clinical practice is a perineometer, which may give women an improved concept of a pelvic floor contraction and provide an effective stimulus to encourage greater and continued effort.

Vaginal weighted cones were introduced by Plevnik (1985). After an explanation of their function, the user is instructed to place the lightest cone into the vagina. Contraction of the pelvic floor is then necessary to hold the cone in place during walking or coughing. Cones of gradually increasing weight are used depending upon the ability of the patient to retain the device in the vagina. A recent randomised controlled study of conservative treatments for GSI has indicated that only 7.5% of women felt they no longer had an incontinence problem after using vaginal cones for six months, and there was no difference in pelvic muscle strength compared to the control group at the end of the study period (Bo et al 1999). Unfortunately, as well as a lack of efficacy cones may produce prolonged isometric contractions of the pelvic floor muscles and muscle injuries due to overuse (Bo 1995b).

Electrical stimulation of the pelvic floor is a widely used treatment for GSI and may be used alone or in combination with PFE's. The most effective and popular form at present is functional electrical stimulation using a vaginal electrode. Sand and colleagues performed a prospective, randomised, double blind trial of 35 women using an active stimulator and 17 controls using a sham device (Sand et al 1995). Pad testing showed that stress incontinence was improved by at least 50% in 62% of patients using an active device compared with only 19% using sham devices ($P<0.01$). Interestingly, a

recent meta-analysis has shown that electrical stimulation is as effective as pelvic floor exercises for the treatment of GSI (Berghmans 1998).

Oestrogen supplementation has also been used as a conservative treatment of genuine stress incontinence. This is considered further in **Chapter six.**

3.4.1.2. Surgical management of genuine stress incontinence

Surgery is the mainstay of treatment for women with severe genuine stress incontinence and those who have failed to improve satisfactorily with conservative measures. Over 100 different surgical procedures have been described which indicates that none have achieved 100% success rates without complications. The choice of operation is influenced by the clinical features and the results of urodynamic investigations. The results of a major review of surgery for GSI (Jarvis 1994) are shown in **Table 3.4.**.

PROCEDURE	SUBJECTIVE CURE	OBJECTIVE CURE
Bladder buttress	80.9	72.0
Colposuspension	89.6	84.3
Bladder neck suspension	77.6	70.0
Sling procedures	82.4	85.3
Injectables	56.4	60.2

Table 3.4.: Results of surgery for genuine stress incontinence. Values given are percentages. Adapted from Jarvis (1994).

It is clear from this review and other work recently published (Black & Downs 1996) that procedures performed through a suprapubic approach, such as a colposuspension, have a longer lasting cure rate than those performed vaginally. However, they also have

a higher complication rate and may not be suitable for elderly women who are frail or unfit for surgery. In this case less invasive procedures such as periurethral injection of collagen or macroplastique (Khullar et al 1997, Monga et al 1999), or insertion of a tension free vaginal tape may be more appropriate (Ulmsten et al 1999).

3.4.2. Detrusor instability

Detrusor instability (DI) is defined by the International Continence Society as "a condition in which the detrusor is shown to contract, either spontaneously or on provocation, during bladder filling whilst the subject is attempting to inhibit micturition" (Abrams et al 1990). In the presence of underlying neurological disease the term "detrusor hyper-reflexia" is used. The most common presenting symptoms are frequency and urgency of micturition, which occur in 80% of patients (Cardozo & Stanton 1980). However, women may present with a variety of different complaints including those listed below:

- Frequency
- Nocturia
- Urgency / Urge incontinence
- Stress Incontinence
- Nocturnal enuresis
- Coital incontinence

The severity and unpredictability of symptoms frequently makes detrusor instability a very distressing condition for the patient with a significant impact on quality of life. In women with DI there is often no obvious underlying cause. However, there are several theoretical reasons why unstable bladder contractions may occur. In

infancy during "potty training" conscious inhibition of the voiding reflex is acquired. It is possible that in some patients DI may be a consequence of poorly learnt bladder control as a child. Indeed, there is a strong association between nocturnal enuresis in childhood and DI presenting in adult life (Whiteside & Arnold 1975). DI may occur in association with bladder outflow obstruction secondary to benign prostatic hypertrophy in men. While primary bladder outflow obstruction in women is relatively rare, a similar situation may occur following colposuspension. Approximately 15% of women develop de novo DI following retropubic bladder neck surgery (Cardozo & Stanton 1979). The finding in this study by Cardozo and Stanton that the incidence of DI is increased after multiple continence procedures suggests that bladder dissection and consequent denervation is an important underlying pathophysiological cause of this problem.

In women with detrusor hyper-reflexia the complex neurological pathways controlling micturition are disrupted, allowing abnormal uninhibited detrusor contractions to occur. It is possible that women with idiopathic DI an underlying neurological deficit is also present but less obvious. It has been postulated that damage to central inhibitory pathways or sensitisation of peripheral afferent terminals in the bladder may unmask primitive voiding reflexes that trigger bladder overactivity (De Groat 1997). Others have suggested that there may be a myogenic basis for DI (Brading 1997). Partial denervation of the detrusor may be responsible for altering the properties of smooth muscle, leading to both an increased excitability and ability of activity to spread between cells, resulting in co-ordinated myogenic contractions of the whole detrusor.

It is important to remember that DI is only one of a number of causes of irritative bladder symptoms and it can only be diagnosed on cystometry. This is considered in detail in Chapter four.

3.4.2.1. Conservative management of Detrusor Instability

The mainstay of treatment for detrusor instability is bladder retraining and medication. Bladder neck surgery is rarely indicated and can in fact have disastrous effects with a deterioration of the patient's condition.

Behavioural therapy in the form of retraining or "bladder drill" is a logical treatment for DI in view of the loss of bladder control, which was acquired during infancy. Treatment is aimed at both unlearning an abnormal voiding pattern and relearning a more appropriate one. Bladder drill was first described as "bladder discipline" by Jeffcoate and Francis (1966). Several studies since then have shown impressive subjective, and sometimes objective, results. Many have used a regime similar to that described by Jarvis (1981), who found the efficacy of bladder drill to be superior to that of drug therapy. This is still used today and described below:

1) Exclude pathology (e.g.) infection, bladder stone.

   Admit to hospital – the treatment can also be performed as an outpatient.

2) Explain rationale to patient.

3) Instruct to void every 1½ hours during the day. The patient must not void between these times; she must wait or be incontinent.

4) Increase voiding interval by ½ hour when initial goal achieved, and continue with 2 hourly voiding etc.

5) Give encouragement.

Frewen (1982) reported that 86% of 150 women with frequency and urgency were symptomatically cured following 3 months of bladder drill. However, Holmes and colleagues (1983) found that 43% of patients had relapsed 3 years after this form of therapy. This was regardless of whether the bladder had been shown to be stable on urodynamics following treatment. Bladder drill is now frequently performed on an outpatient basis, often in combination with drug therapy. Limitation of fluid intake to 1500ml/24 hours, and avoidance of tea, coffee and alcohol can also be beneficial.

Maximal electrical stimulation can be used for both the treatment of genuine stress incontinence and detrusor instability. Pudendal nerve stimulation, using either a vaginal or anal electrode, has been shown to result in inhibition of the detrusor and relaxation of the bladder. Wise and co-workers (1992) performed a comparative trial of maximal electrical stimulation and oxybutynin. In both groups there was a significant reduction in urinary symptoms using a visual analogue scale, and a reduction in frequency using a urinary diary. However, electrical stimulation appeared to be more acceptable to the women in the study. This form of treatment is currently mainly performed by continence advisors, specialist nurses and physiotherapists often in combination with other therapies.

Drug therapy is probably the most frequently used treatment for DI. Until recently oxybutynin hydrochloride (a compound with antimuscarinic, spasmolytic and local anaesthetic properties) has been the medication of first choice. The first double blind, placebo controlled study of 30 patients was reported in 1980 (Moisey et al 1980). Of the patients treated with oxybutynin, 60% were symptomatically improved compared to 8% of those on placebo. Unfortunately, oxybutynins use is limited by a lack of specificity and anticholinergic side effects of dry mouth, blurred vision and constipation. As many of these symptoms are caused by a metabolite of oxybutynin,

produced in the liver following oral therapy, other routes of administration (such as vaginal, rectal and intra-vesical therapy) have been tried with varying degrees of success. Other anticholinergic medications such as probantheline and imipramine have also been proven to be useful treatments for DI but unfortunately they have a similar side effect profile to oxybutynin.

Several subpopulations of muscarinic receptors have been identified at least five different subtypes (M1-M5) have been cloned. Receptor studies have shown that there is a predominance of M3 receptors in the human detrusor compared to other subtypes (Andersson 1997). Tolterodine is a new potent competitive muscarinic receptor antagonist developed for the treatment of the overactive bladder. This compound was selected for development with the objective of achieving separation of the antimuscarinic effects on the bladder and salivary glands. A number of studies have compared the efficacy of tolterodine with oxybutynin. It has been demonstrated that the two compounds are equipotent at bladder muscarinic (M3) receptors. However, radioligand binding data show that tolterodine has 8 times less potency than oxybutynin at the muscarinic receptors in the parotid gland.

Appell (1997) has recently published a pooled analysis of the safety, efficacy, and tolerability of tolterodine in 4 randomised 12-week studies of patients with an overactive bladder. It was shown that tolterodine significantly reduced the number of incontinent episodes and increased the volume voided/micturition compared to placebo. In addition, adverse events were tolerated significantly better than those due to oxybutynin.

3.4.2.2. Surgical management of detrusor instability

Many different surgical techniques have been used to treat DI but few have produced effective long-term results and all are associated with significant complications. Vaginal denervation (Ingelman-Sundberg 1978), bladder transection (Turner-Warwick & Ashken 1976), bladder distension (Dunn et al 1974), subtrigonal injection of phenol (Ewing et al 1982) and other procedures have all been introduced enthusiastically at varying times but few are in regular use today.

For those women with extremely severe DI refractory to all other therapies an augmentation "clam" cystoplasty or urinary diversion may be appropriate.

3.4.3. Frequency and urgency

The urinary symptoms of frequency and urgency (also known as irritative symptoms) may occur in women of all ages but they are particularly common following the menopause. There are many pathological causes of these complaints (**Table 3.5.**) which may occur alone or in combination with other problems such as nocturia, dysuria or incontinence. Treatment primarily depends upon the aetiology of the patient's symptoms, which is almost always diagnosed by investigation (**Chapter four**).

Women who drink excessively can be helped to modify their intake provided a metabolic cause for their thirst such as diabetes mellitus is excluded. A frequency/volume chart can sometimes be useful to indicate to the patient their abnormal drinking habits and bladder retraining can also be helpful. Urinary tract infection should be treated with antibiotics, based on the urine culture and sensitivity results. When the standard urine culture is negative it is sometimes worth examining the urine for fastidious organisms including Mycoplasma hominis and Ureaplasma Urealyticum (Boos et al 1997).

Patients with GSI or DI should be treated as described earlier. Women with impaired bladder emptying are usually treated with a combination of double voiding, cholinergic medication and sometimes intermittent or indwelling catheterisation depending upon the severity of their condition. Women with chronic inflammation of the bladder mucosa (chronic cystitis) are often difficult to treat satisfactorily. Pain is the presenting complaint in 70% of patients (Koziol 1994) but usually women have a number of different symptoms which often vary in their intensity. Urinary tract infection may previously have been diagnosed but often urine culture is negative. Clinical examination is often unrewarding but sensory urgency is usually diagnosed on cystometry. Cystoscopy with bladder base biopsy must be undertaken to confirm the diagnosis. Some women with severe bladder inflammation may be diagnosed as having interstitial cystitis, the aetiology of which is poorly understood (Toozs-Hobson & Cardozo 1996). However, treatment is usually as per other causes of this condition. In view of the possible underlying infective process, regardless of the results of urine culture, long-term antibiotics are often prescribed. Norfloxacin 400mg daily for three months is currently the most effective and has few side effects. Alternatively, a bladder antiseptic such as hexamine hippurate may be used. Other treatments such as anticholinergic or anti-inflammatory medication, local anaesthetics, dimethylsulphone (DMSO) and bladder distension have all been tried with varying degrees of success. The number of treatment options available provides an indication that few are effective in treating this condition which frequently runs a chronic and relapsing course.

The role of oestrogen in the pathophysiology and treatment of irritative bladder symptoms is discussed fully in **Chapter six.**

- **Psychosocial**

(e.g.) Excessive fluid intake
Habit
Anxiety

- **Urological**

(e.g.) Urinary tract infection
Detrusor instability (detrusor hyper-reflexia)
Genuine stress incontinence
Impaired bladder emptying
Small capacity bladder
Chronic cystitis (interstitial cystitis)
Urethral syndrome
Intravesical pathology (stones, papilloma, tumour)
Tuberculosis

- **Gynaecological**

(e.g.) Pregnancy
Prolapse
Pelvic mass (Fibroids, ovarian tumour)

- **Sexual**

(e.g.) Coitus
Sexually transmitted disease

- **Medical**

(e.g.) Diuretic therapy
Congestive cardiac failure
Impaired renal function
Neurological disease

- **Endocrine**

(e.g.) Diabetes mellitus
Diabetes insipidus

- **Oestrogen deficiency and the menopause**

Table 3.5.: Common causes of female urinary frequency and urgency.

CHAPTER 4

INVESTIGATION OF LOWER URINARY TRACT DYSFUNCTION

4.1. INTRODUCTION

When assessing a woman who presents with lower urinary tract symptoms it is important to take an accurate history and perform a detailed examination. However, it is now widely accepted that there is a poor correlation between a patient's symptomatology and the underlying pathophysiology (Bates et al 1970, Cardozo & Stanton 1980, Jarvis et al 1980, Lagro-Janssen et al 1991b). If therapeutic decisions are based on symptoms alone then more than 25% of patients may be treated with inappropriate and potentially harmful therapy. In this chapter the investigations used for the evaluation of women with lower urinary tract symptoms are outlined.

4.2. BASIC / OFFICE INVESTIGATIONS

4.2.1. Mid-stream urine (MSU) sample.

Urinary tract infection (UTI) may cause or exacerbate urinary symptoms. The results of urodynamic investigations will also be invalidated if tests are performed when the patient has a UTI. A mid-stream sample of urine must therefore be taken from all women presenting with urinary symptoms. A detailed account of urine culture and the role of urinary tract infection in postmenopausal women is given in **Chapter eight.**

4.2.2. Frequency-volume charts

While a clinical interview may provide some information on the voiding habits of a patient the impression of symptom severity obtained is largely subjective and to some extent retrospective in nature. Patients tend to exaggerate their urinary symptoms when giving a history (Wyman et al 1988) and their recall of incontinent episodes may not be reliable.

The frequency volume chart (also known as a urinary diary) provides an objective assessment of a patient's fluid input and urine output. An example of the chart used in this thesis is shown in the **Appendix**. The instructions given to the patients are shown on the reverse side. As well as the number of voids and incontinence episodes, the mean volume voided over a 24 hour period can also be calculated. Frequency volume charts have the advantage of assessing symptom severity in the individual's own environment under normal conditions.

Self monitoring techniques may themselves modify the behaviour they are measuring (Verbrugge 1980). However, reported micturition frequency and the number of incontinent episodes have been found to be highly reproducible on test-retest analysis (Wyman et al 1988, Larsson & Victor 1988). There is some controversy regarding the optimum duration that the charts should be completed for. A balance needs to be reached between asking the patient to complete a diary for a long time period, which may possibly increase its reliability, and the inconvenience of doing so. Current practice is to ask the patient to complete the chart for at least 5 days. Wyman and colleagues (1988) compared the results obtained in each week of a two week diary. There was a strong correlation between the two weeks, suggesting that it is acceptable for the patient to complete a diary for seven rather than 14 days. Larsson and Victor (1988) studied 151 asymptomatic women aged 19-81 years who agreed to complete a frequency volume chart over a 48 hour period. The voiding characteristics of the women in this study are shown in **Table 4.1.**. Only 8% had a micturition frequency of eight times or more in 24 hours with a tendency for the number of nocturnal micturitions to increase with age. Unfortunately, in symptomatic women it is not possible to reliably distinguish patients with genuine stress incontinence

from those with other urodynamic diagnoses using frequency volume charts alone (Barnick 1997).

PARAMETER	MEAN	SD	RANGE
Frequency / 24h	5.8	1.41	3-11
Mean volume voided (ml)	250	79	90-610
Largest single volume voided (ml)	460	174	200-1250

Table 4.1.: Normal frequency / volume chart data. Adapted from Larsson and Victor (1988). Note the large standard deviation and range of the largest single volume voided which limits the usefulness of this parameter.

4.2.3. Pad test

A simple way of measuring the quantity of urine lost due to incontinence is to compare the difference in weight of a perineal pad before and after its use. This is usually done with a standardised volume of fluid in the bladder over a predetermined time period. The technique is particularly useful in a research setting to objectively study the effectiveness of treatments for stress incontinence. However, it was not an appropriate tool for the studies in this thesis and therefore it is not considered further.

4.3. SYMPTOM QUESTIONNAIRES AND QUALITY OF LIFE INSTRUMENTS

Obtaining details of a patient's urinary symptoms and their severity can be done in a number of different ways. Taking a history is the most commonly used method in clinical practice but the information obtained is largely subjective and open to significant bias. Changes in specific symptoms in response to treatment may also be difficult to determine particularly if the patient is seen by a number of different clinicians over a long time period. This technique is therefore not considered a reliable way to obtain information in a research setting. Self completed questionnaires also need to be used cautiously as they rely on the patient's full comprehension of the terms used.

Direct questioning using a structured questionnaire has the advantage that information is collected in a systematic and consistent way. Questionnaires of this type are often used in conjunction with visual analogue scores (VAS). The format of the VAS used in this thesis utilises a straight line 10cm long (**Appendix**). One end (0cm) represents the complete absence of a particular symptom and the other end (10cm) the maximum severity of that complaint. The patient is asked to mark on the line their perception of the severity of each symptom and a numerical value is determined by measuring the distance in centimetres of the mark from the 0cm position (Altman 1991). One of the main disadvantages of this system is that few women mark directly on the 0cm position to indicate that this symptom is absent, and therefore a falsely high score may be obtained. However, VAS are easily understood by most patients, quick to complete and provide a simple objective way to assess both symptom severity and the changes that may occur following treatment.

It is now widely acknowledged that the impact of urinary symptoms cannot be fully described by measures of disease status such as simple questionnaires or the results of complex investigations (Kelleher et al 1995, Muldoon et al 1998). Indeed, a poor correlation has been found between the subjective degree of bother that symptoms cause and objective measures of the degree of urinary incontinence (Wyman et al 1987, Ryhammer et al 1995). Psychosocial factors such as the impact on normal functioning, social and personal relationships, emotional wellbeing and satisfaction with everyday life also need to be taken into account. Quality of life (QoL) instruments have therefore been developed to measure the abstract concept of an individual's perceived level of physical, psychological and social wellbeing (Kelleher et al 1995). There are two main types of QoL questionnaire, each containing a number of sections (also known as domains) which focus on particular aspects of health.

Firstly, generic questionnaires (e.g.) Short Form 36, Nottingham Health Profile and the Sickness Impact Profile which measure general health status. These measures have been developed to assess overall function and are useful for evaluating the health of different populations. However, they are relatively insensitive measures of the effect urinary symptoms on QoL and its improvement after treatment (Kelleher et al 1997). For example, there is no strong correlation between stress incontinence and generic QoL, although there does appear to be some correlation for urge incontinence (Hunskaar & Vinsnes 1991, Grimby et al 1993).

Secondly, disease specific questionnaires (e.g.) Incontinence Impact Questionnaire and King's Health Questionnaire which assess the impact of particular conditions on QoL. This type of measure offers greater sensitivity for evaluation of the severity of specific

conditions and is therefore more applicable to use in clinical trials. In this thesis the King's Health Questionnaire (Kelleher et al 1997) was used to assess the impact of urinary symptoms on QoL. The questionnaire and scoring system (**Appendix**) were generated after seven different pilot versions had been tested on over 500 women. There are 30 questions divided into eight sections as follows:

1. General health perceptions.
2. Urinary symptoms.
3. Role limitations.
4. Physical / social limitations.
5. Personal relationships.
6. Emotions.
7. Sleep-energy disturbance.
8. Incontinence impact.

The King's Health Questionnaire has been shown to be a valid and reliable instrument sensitive to changes in lower urinary tract symptomatology and useful for evaluating treatment outcome. Women of all ages and intellectual ability find it easy to understand and answer with over 97% of the women tested by Kelleher (1997) completing it correctly.

QoL is an abstract and highly subjective concept influenced by personal and cultural values, goals, age, life expectancy and a broad range of different experiences (Kelleher et al 1997). While duration of symptoms and quantity of urine lost do not appear to

significantly effect QoL scores (Wyman et al 1990) the underlying cause of a patients urinary complaint is a major factor in predicting the extent of QoL impairment. Detrusor instability has a greater overall impact on almost all domains of QoL than genuine stress incontinence, presumably because the condition is less predictable in nature and the women have less control over their bladder symptoms (Wyman et al 1987, Kelleher et al 1997). The main exception to this is the finding that women with genuine stress incontinence have higher scores in the domain of incontinence impact.

4.4. URODYNAMIC INVESTIGATIONS

4.4.1. Uroflowmetry

Uroflowmetry is the simple and non-invasive measurement of urine flow. To obtain a representative record of flow parameters the woman is asked to void in private when her bladder is comfortably full. Several types of flowmeter can be used but the commonest are those with either a strain gauge weighing transducer placed under a receptacle into which the patient voids or devices with a disk which rotates at a speed dependant upon the flow of urine (Cutner 1997). The signals produced are electronically converted and smoothed to give visual representation of a patient's urinary flow. A normal flow pattern is shown in **Figure 4.1.**. The maximum flow rate and volume voided are recorded and an estimation of the postmicturition residual determined either by catheterisation or using ultrasound.

In most circumstances in adults a voided volume of less than 150 ml cannot be interpreted reliably while flow rates obtained above 500 ml may also be low, perhaps due to decompensation as the bladder capacity is reached (Abrams et al 1983). The normal flow pattern is bell shaped with a maximum flow rate of at least 15ml/s. If a woman has a

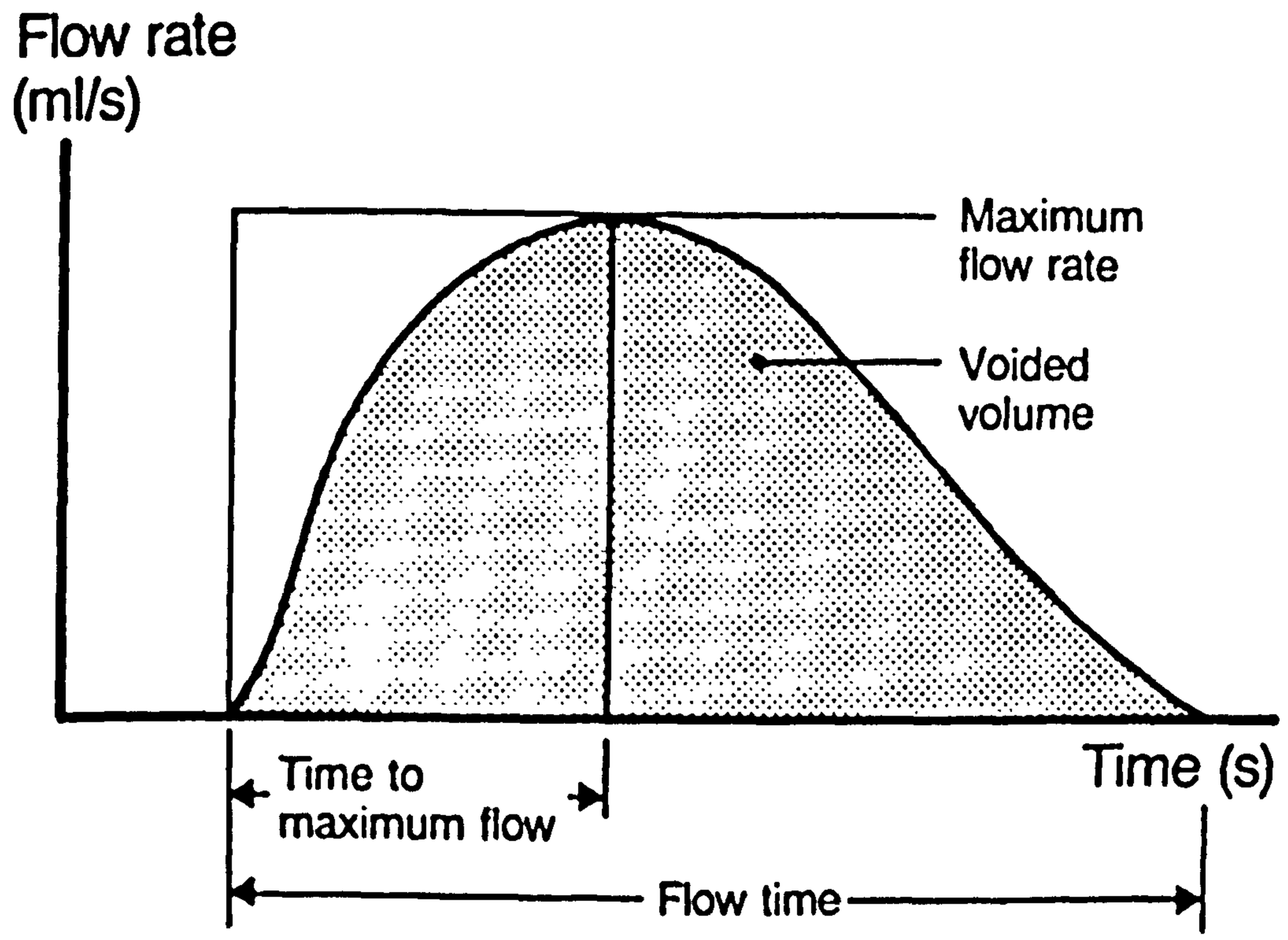


Figure 4.1.: Normal uroflowmetry study with ICS recommended descriptive terminology.

prolonged void, reduced flow rate and evidence of abdominal straining then it is possible that she may have voiding difficulties, particularly if these findings are accompanied by a post-micturition residual of more than 50ml. However, it is usually necessary to repeat the assessment at least once as some women may develop this pattern of voiding if they are embarrassed by the test itself and find it difficult to pass urine in unusual surroundings.

A reduced flow rate simply gives an indication that a woman may have a voiding problem. However, it gives no information as to whether this is due to an impaired detrusor contraction or bladder outflow obstruction. Uroflowmetry is therefore often considered in conjunction with a pressure flow study obtained during voiding cystometry as described below.

4.4.2. Cystometry

Measurements of bladder pressure and urine flow have been made for several decades but with advances in electronic technology and equipment urodynamic investigation has assumed greater importance. The aim of cystometry is to reproduce the patient's symptoms and give a pathophysiological explanation of her problem. The cystometrogram (CMG) is used to measure several features of bladder behaviour including sensation, capacity, compliance, contractility and urethral function. The collection of this information has been standardised by the International Continence Society (ICS) (Abrams et al 1990).

Several steps are involved in performing a cystometrogram (CMG):

1. **Insertion of pressure transducers and filling catheter.**
2. **Filling cystometry.**
3. **Voiding cystometry.**

In general, the patient should not be taking medication which may affect bladder function (particularly anticholinergics) as this may alter the results of the cystometrogram and as stated earlier there must be no evidence of urinary tract infection

4.4.2.1. Insertion of pressure transducers and filling catheter

Pressure measurements are made by external transducers connected to the patient by either solid state transducer catheters or fluid filled catheters (the later are used at King's College Hospital). To assess these different components of bladder behaviour the following measurements are required:

1. **Intravesical pressure (*pves*)** which is the total pressure in the bladder.
2. **Intraabdominal pressure (*pabd*)** which is taken to be the pressure surrounding the bladder.
3. **Detrusor pressure (*pdet*)** which is the component of intravesical pressure created by active and passive forces in the bladder wall. It is calculated automatically by most urodynamic equipment using the equation: ***Pdet = pves - pabd***

Almost all units pass a pressure catheter transurethrally into the bladder to measure *pves* and a rectal catheter to measure *pabd*. A filling catheter is also inserted into the bladder at the same time. Urethral catheters do slightly distort the normal anatomy (Tessier & Schick 1990), and therefore suprapubic catheters have been suggested as a superior alternative (Rollema et al 1990). However, they are more painful and difficult to insert and probably associated with higher morbidity than pressure catheters inserted transurethrally. It is currently thought that fine fluid filled pressure catheters (4.5F) have little clinically significant effect on bladder outlet

mechanics, and the larger diameter catheters (12F) which are used for filling the bladder are removed before a patient is asked to void at the end of the study.

To reliably determine detrusor pressure all systems must be zeroed at atmospheric pressure and air bubbles must be thoroughly flushed out of the lines prior to commencing recording. At the beginning of the study the patient is asked to cough, thereby causing a rise in intra-abdominal pressure which is demonstrated by a rise in both intravesical and rectal pressure. The rise in *pves* and *pabd* should be identical and therefore the electronically subtracted *pdet* will remain flat. To ensure that the pressure in the bladder and rectum continues to be recorded satisfactorily during filling checks are made at regular intervals, usually by asking the patient to cough after every 100ml of fluid has been infused. Similarly, after completing the voiding CMG, before removal of the pressure transducers, it is essential to ensure that they have not been dislodged during the void and are still recording pressure changes reliably by asking the patient to cough once more.

4.4.2.2. Filling cystometry

In most units the bladder is filled with fluid which has been stored at room temperature. For simple cystometry normal saline is generally used but for those patients where the bladder needs to be imaged X-ray contrast (Isopaque) is given instead. This later technique is then called videocystourethrography (VCU). In its report the ICS has defined bladder filling as fast (>100 ml per minute), medium (10-100 ml per minute) and slow (up to 10 ml per minute). It should be noted that even the ICS slow fill rate is unphysiological and much quicker than could be expected normally, except under extreme diuretic conditions.

In this thesis all patients underwent VCU in the X-ray department using a standardised technique. After insertion of the filling catheter and pressure lines, and measurement of the urinary residual, the bladder was filled with Isopaque at 100 ml per minute (using a computer controlled pump) with the woman in the supine position. The woman was asked to indicate when she first had a desire to pass urine, and the pressure and volume of fluid in the bladder were recorded. Although subjective in nature this *first sensation* to pass urine can then be described as normal, early/reduced if the volume in the bladder is less than normal or increased/absent if above the normal range. This later finding may be associated with a bladder of large capacity, chronic urinary retention or neurological disease although commonly it is idiopathic. Bladder filling was continued until the woman had developed a strong desire to void or 500 ml of contrast had been infused. The pressure and volume were again noted and recorded as the *maximum bladder capacity*. While it may be possible to fill the bladder beyond a volume of 500ml, this may result in unnecessary discomfort for the patient and produce artefacts secondary to overfilling. The normal ranges for filling cystometry are shown in **Table 4.2.**.

PARAMETER	RANGE
Postmicturition residual	0-50ml
First sensation to void	150-250ml
Maximum bladder capacity	400-600ml

Table 4.2.: Normal ranges for filling cystometry. Adapted from Benness (1997).

During the filling phase the pressure in the bladder is constantly recorded. In the normal physiological state the bladder is a low pressure storage unit and as described in **Chapter two,** the pressure does not normally rise until its absolute capacity is reached. This is described as normal *compliance* and the bladder is regarded as being *stable.* Rapid filling of the bladder during cystometry may produce a rise in detrusor pressure which is termed *low compliance.* In the urogynaecology unit at King's College Hospital this is diagnosed when the pressure at the end of filling is greater than 15cmH_2O. As the compliance of the bladder is a function of the change in pressure for a change in volume it is important clinically to consider the volume in the bladder when the pressure rises above this level. If this finding occurs with less than 350ml in the bladder it is felt to be clinically significant, while small rises at the end of filling may simply be regarded as an artefact of the test, particularly if the patient has a large bladder capacity. This area is controversial and there is disagreement between different units as to its measurement and interpretation. In our unit the pressure at the end of filling is considered the most significant. However, sometimes the pressure in a low compliant bladder falls a few seconds after filling is stopped, and although the pressure is then lower it is still above the normal range. This second measurement is recorded in some other centres.

Causes of reduced bladder compliance include detrusor muscle hypertrophy, which may be associated with detrusor instability or bladder outflow obstruction, particularly in men in association with prostatic hypertrophy. In women this is most commonly seen after surgery for stress incontinence. Hypertrophied muscle is less elastic than normal detrusor smooth muscle and also synthesises more collagen, resulting in an increase in stiffness. Ageing may also result in partial replacement of bladder smooth muscle with collagen. Women with low bladder compliance have an

increased incidence of detrusor instability on ambulatory monitoring, suggesting that in some women the underlying pathology may be similar if not the same. A schematic diagram of a normal cystometrogram and one showing low compliance is shown in **Figure 4.2.**.

At the end of filling, the filling catheter is removed and the X-ray table rotated so that the bladder can be imaged with the patient standing. A series of provocative manoeuvres are then performed. This initially takes the form of one, three and then five coughs while the bladder is imaged to see if any incontinence occurs. Women who leak with the first cough are graded as having severe incontinence, those during a series of three coughs moderate leakage and women who only leak at the end of five coughs mild incontinence. The grading of incontinence may be changed depending upon the actual quantity of urine lost and is not solely dependent upon the timing in relation to the provocative tests. If the patient's main complaint is of incontinence and there is no demonstrable leakage after coughing, other provocative manoeuvres such as star jumps, hand washing and listening to running water may also be necessary to demonstrate objective evidence of urinary leakage. It is vital that the detrusor pressure at the time a patient is incontinent is noted as this is of prime importance when trying to determine if the patient has underlying detrusor instability or genuine stress incontinence as the main cause of their problem.

Detrusor instability (DI) is characterised by involuntary bladder contractions which occur during the filling phase. These may be spontaneous or provoked and cannot be completely suppressed by the patient. Any associated leakage of urine is called *urge incontinence.* Provocation may include rapid filling, alterations in posture or movement such as standing, tap running and coughing. Detrusor instability results in phasic contractions, which should be contrasted with altered compliance where the

detrusor pressure rises gradually (**Figure 4.2.**). There is at present no accepted method for quantification of detrusor contractions and it is unclear what the effects of posture and filling speed on the detection of detrusor instability are. Originally, it was suggested that clinical judgement should be exercised regarding the significance of phasic contractions of less than 15cmH_2O in amplitude, but currently no lower limit is specified (Abrams et al 1990) as the relationship to the patient's symptoms is considered to be more important. If detrusor instability is present and there is objective evidence of a relevant neurological disorder, the instability may be termed *detrusor hyperreflexia*. A diagnosis of *sensory urgency* is made when initial catheterisation is painful, there is an early first sensation to void and a reduced bladder capacity. Although the patient usually complains of urgency during the test there is no rise in detrusor pressure.

Genuine stress incontinence (GSI) is the involuntary loss of urine which occurs in the absence of a detrusor contraction. This is normally demonstrated during the provocative manoeuvres at the end of filling cystometry. Typically, such loss of urine occurs instantaneously and examination of the subtracted detrusor pressure should confirm that there is no associated cough induced detrusor instability before making the diagnosis of GSI.

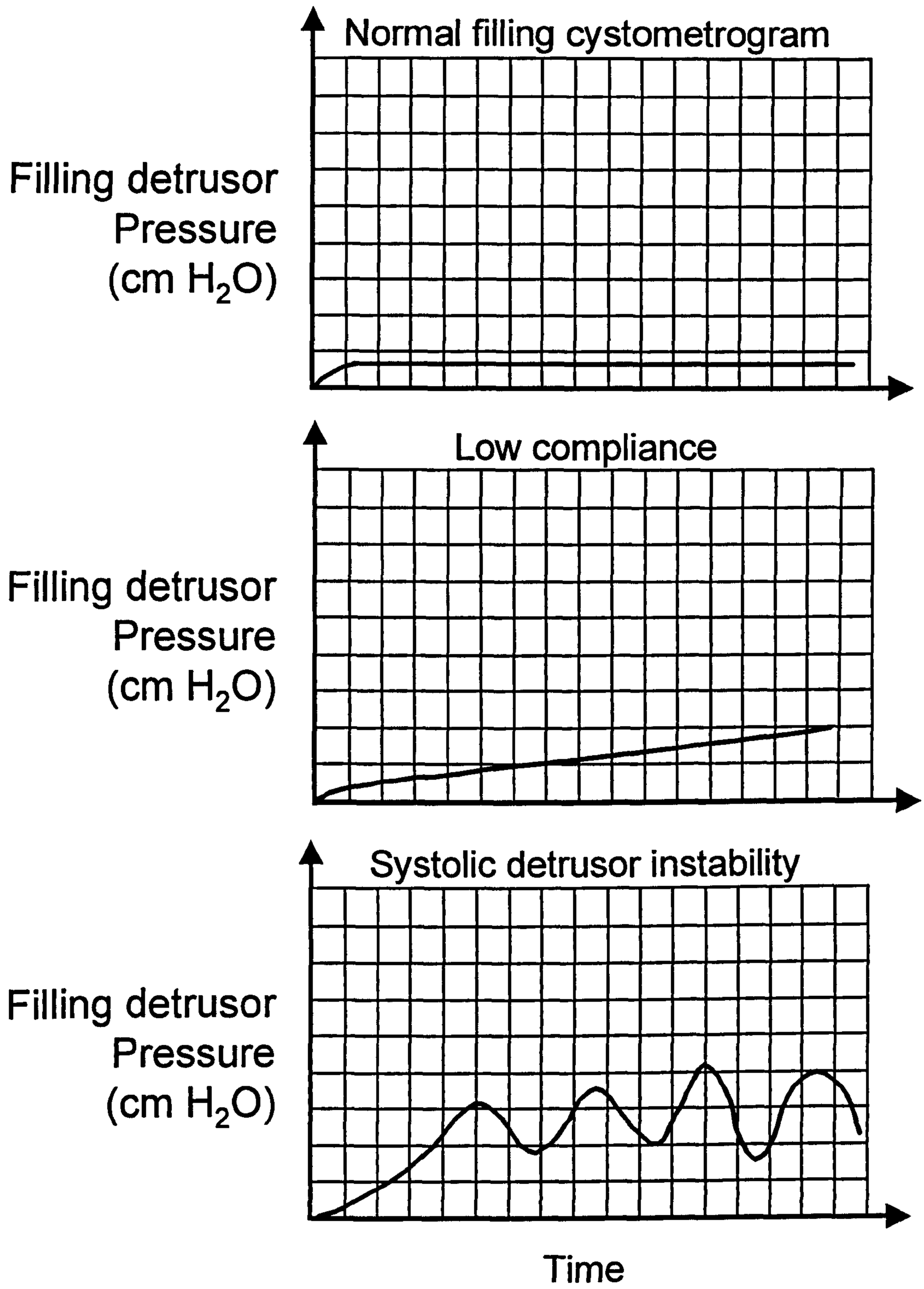


Figure 4.2.: Cystometrogram patterns of filling detrusor pressure.

4.4.2.3. Voiding cystometry

Having performed filling cystometry the CMG is completed with a voiding study. As previously indicated the filling catheter is removed prior to voiding to prevent any unnecessary urethral obstruction. The intravesical and rectal pressure recording lines are left in situ, allowing simultaneous measurement of detrusor pressure along with urine flow. As with uroflowmetry, the patient is asked to void while sitting on a flowmeter in private.

During normal voiding there is a co-ordinated contraction of the bladder and at the same time relaxation of the urethra which is sustained until the bladder is empty. Women normally void with a detrusor pressure rise of less than 60cmH_2O and a peak flow rate of > 15ml/s for a voided volume of at least 150ml (Benness 1997). Some women have an excellent flow of urine with little or no rise in detrusor pressure which is simply a reflection that the contraction has occurred in the presence of low outlet resistance. However, if the detrusor pressure during voiding is reduced with low flow rates and a significant post-micturition residual the patient is classified as having a *voiding difficulty*. In women, voiding problems are rarely due to bladder outflow obstruction and much more likely to be secondary to impaired detrusor contractility. Bladder outflow obstruction is characterised by a low flow rate and raised detrusor pressure during voiding. The patient may also be seen to use additional abdominal straining to try and improve the intravesical pressure. The situation is further complicated by the fact that in some women with outflow obstruction the detrusor decompensates with time, resulting in both a low detrusor pressure and low flow rate (Cutner 1997). Pressure flow measurements can be plotted graphically but the use of this technique in urogynaecological practice is not established and therefore not included in this review.

In some women, and particularly those with overt neurological disease, pathological contraction of the external sphincter occurs during a bladder contraction. This is termed *detrusor sphincter dyssynergia* (DSD). Characteristically there is a high detrusor pressure during voiding associated with a poor flow rate. In some women urinary retention may occur and catheterisation is therefore necessary. It must be remembered that both sphincteric relaxation and initiation of voiding are subject to powerful cortical influence, so the results of urodynamic investigation may be confounded by embarrassment or an unfamiliar testing environment. Most patients are able to pass urine at the end of the study, but their inability to do so does not necessarily indicate a functional abnormality. Some women will subsequently have free flow rates and residual urine assessments which indicate normality.

At King's College Hospital almost all women presenting with lower urinary tract symptoms undergo videocystourethrography at their first clinic appointment. While this enables an early accurate diagnosis to be made, it is recognised that for many patients it is an embarrassing investigation with approximately 27% of women also finding the procedure painful (Gorton & Stanton 1999). In addition, there is a small (approximately 2%) risk of causing a urinary tract infection (Walter & Vejlsgaard 1978). To try and reduce this risk women are advised to increase their fluid intake in the 48 hours after urodynamic investigation. Cystometry has been criticised as being unphysiological. For this latter reason ambulatory urodynamics have been introduced. However, this investigation was not used in this thesis and therefore it is not described further.

4.4.3. Urethral pressure profilometry

The resting urethral pressure profile (UPP) is a graphical record of pressure within the urethra at successive points along its length. A number of measurements can be taken as shown in **Figure 4.3.**, allowing an objective comparison of urethral function both between patients and also before and after different treatments. Although the concept of measuring the UPP appears physiological there is considerable uncertainty regarding its predictive value. Several authors have shown significant differences in urethral parameters between stress incontinent and continent women (Hilton & Stanton 1983a, Bump et al 1988). However, the standard deviation of values around the mean is so large that the degree of overlap between continent and incontinent women severely limits its clinical usefulness.

The following technique was used to obtain a urethral pressure profile from the women in this thesis. After cystometry had been completed, the patient was asked to lie supine on the X-ray table. The bladder was again filled to 250ml with normal saline using a urethral filling catheter, which was then removed. A catheter mounted solid state pressure transducer was then passed into the bladder with the two transducers (which are 6cm apart) directed to the 9 'o'clock position. Both intravesical pressure and urethral pressure were recorded simultaneously to ensure that any changes in urethral pressure were not caused by an abnormal detrusor contraction. The catheter was withdrawn at a set speed and the procedure repeated to ensure the reproducibility of the profile obtained.

Finally, after the catheter had again been reinserted the patient was asked to give a series of coughs at one second intervals as the catheter was withdrawn to obtain a stress urethral profile. The principle of this test is to measure the pressure transmission ratio (PTR) from the abdominal cavity to the urethra. Pressure transmission ratios

provide a dynamic assessment of the response of the urethra to raised intra-abdominal pressure. In women with genuine stress incontinence the pressure transmitted to the urethra is often inadequate. However, as with the resting urethral pressure profile the specificity of the PTR is poor (Versi 1990, Rosenzweig et al 1991). The PTR is calculated using the formula:

PTR = Urethral pressure / Bladder pressure x 100

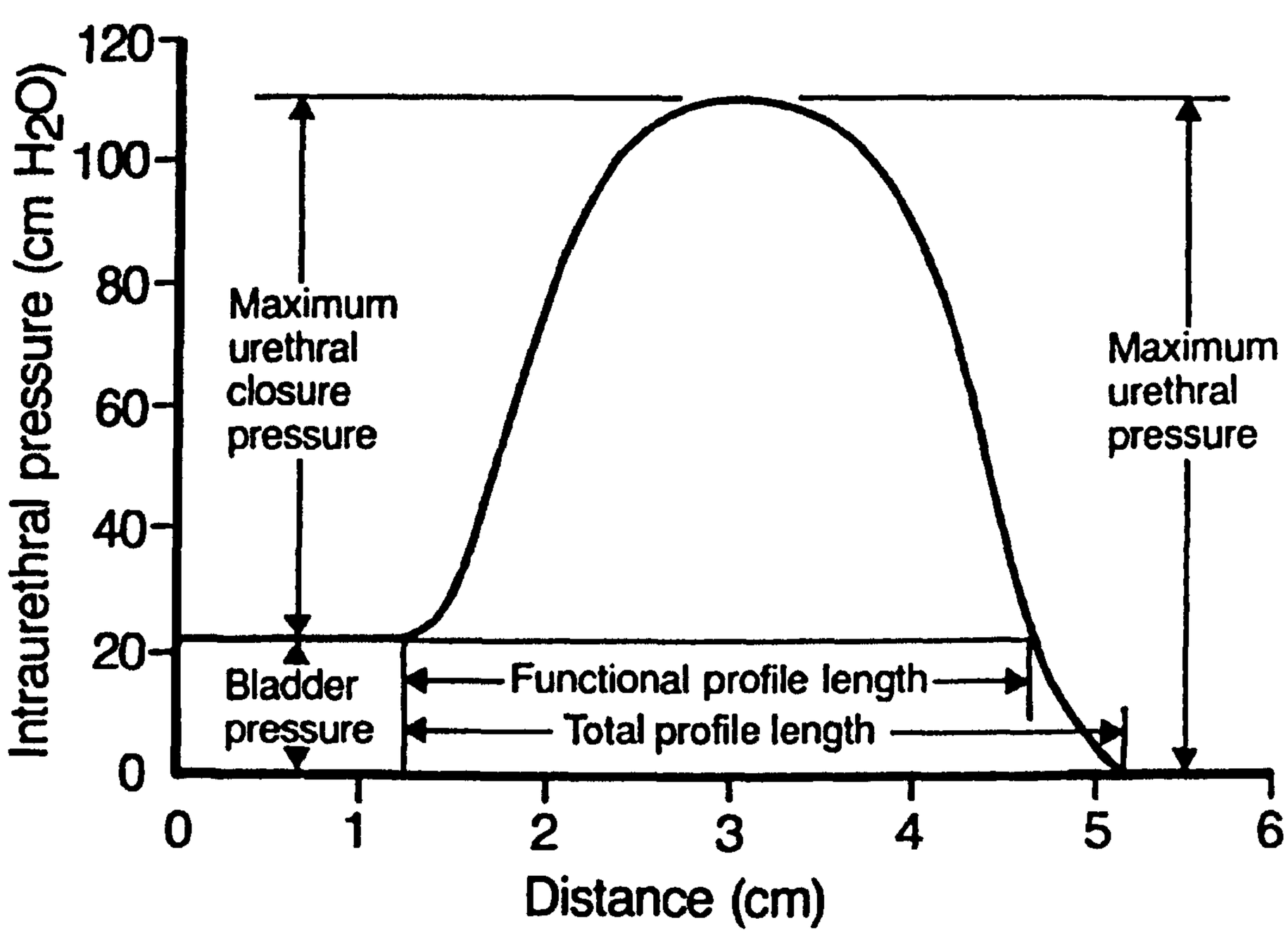


Figure 4.3.: Theoretical urethral pressure profile (UPP).

CHAPTER 5

OESTROGEN, THE MENSTRUAL CYCLE AND THE MENOPAUSE

5.1. OESTROGEN

The three natural oestrogens in women are oestrone (E_1), oestradiol (E_2) and oestriol (E_3), all derivatives of the basic cyclopentophenanthrene steroid nucleus (**Figure 5.1.**).

Oestrogens may circulate in three forms:

1. Free
2. Protein bound
3. Conjugated

Free oestrogens are lipophilic, freely traverse cell membranes and are therefore biologically active. Over 95% of circulating oestrogens are protein bound, primarily in a complex with albumin or sex hormone binding globulin (SHBG), and presumed to be biologically inactive. Oestrogens are conjugated in the liver as sulphates or glucoronates, which are water soluble and excreted in the urine or bile.

Free oestrogens exert their metabolic effect by binding to high affinity oestrogen receptors in the nucleus of the target cell (King & Greene 1984, Welshons et al 1984). The hormone receptor complex initiates the production of messenger RNA (mRNA) and protein synthesis is observed several hours following oestrogen administration. The potency of a specific oestrogen depends primarily on the length of time the steroid receptor complex occupies the nucleus of the target cell. Of the natural oestrogens, oestriol exhibits the shortest occupancy of the nucleus (1-4 hours) and is therefore considered to be a "weak oestrogen" if given in a single dose. The other natural oestrogens exhibit an intermediate nuclear retention of 6-24 hours (Clark et al 1978). Oestradiol is found mainly before the menopause as its serum concentration falls when

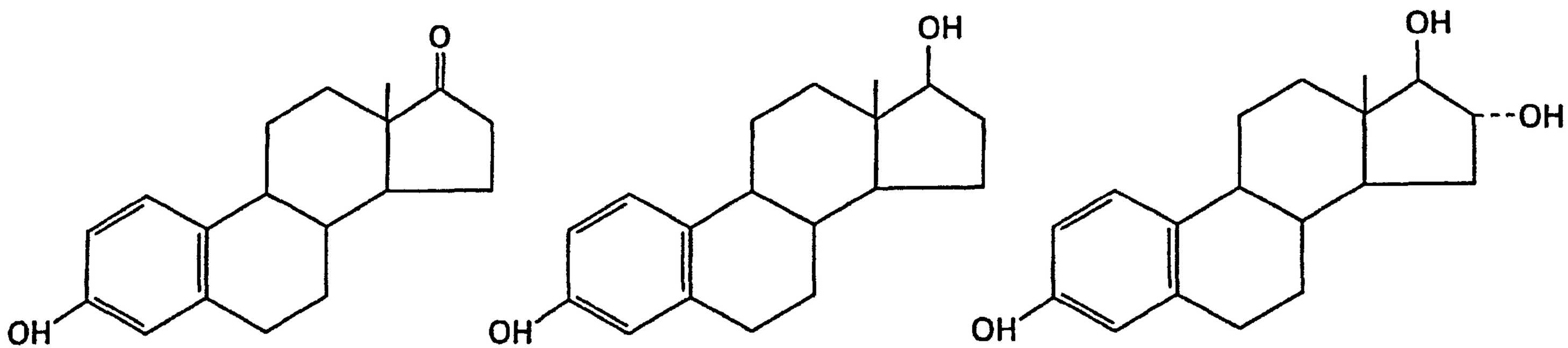


Figure 5.1.: The three natural oestrogens in women. All are derivatives of the basic cyclopentophenanthrene steroid nucleus.

ovarian follicular development ceases. Oestrone is the main oestrogen found after the menopause and is produced by conversion of adrenal androgens in peripheral fat.

The relative potency of the various oestrogenic preparations clinically available is determined by multiple factors including the dose and route of administration, the efficiency of absorption and metabolic clearance, and the particular system or effect under evaluation. This is considered in more detail later in this chapter. As well as an action mediated through oestrogen receptors, recent work has also suggested that oestrogens may have a direct (non-genomic) mechanism which is outlined in **Chapter six.**

5.1.1. Measurement of serum oestradiol

In this thesis serum oestradiol was measured using a Heterogeneous Competitive Magnetic Separation Assay (MSA). Blood samples were taken by myself with the analysis being performed by laboratory technicians, as the instrumentation required could only be operated by trained staff in the Department of Biochemistry at Kings College Hospital (Personal Communication, Dr R Sherwood, Principal Biochemist, Kings College Hospital). The assay has a range of 30 – 13 212 pm/L. To ensure accuracy internal controls are analysed at regular intervals throughout the day. In addition, every month five control samples are received from an external laboratory. A satisfactory level of performance is achieved when the analyte values obtained for each control are within acceptable control ranges (normally +/- 2 standard deviations of the assigned value).

5.2. THE MENSTRUAL CYCLE

The human menstrual cycle is under the control of follicle stimulating hormone (FSH) and luteinizing hormone (LH) secreted from the anterior pituitary gland. FSH, as its name suggests, is responsible for the early stimulation and growth of ovarian follicles. LH may contribute to follicular growth and oestrogen production but its principle actions are to cause ovulation and convert the ruptured Graafian follicle to a corpus luteum. FSH and LH are glycoproteins with a molecular weight of about 30 000. Each consists of two non-identical subunits – alpha and beta. The alpha unit is similar in all pituitary glycoproteins and human chorionic gonadotrophin (HCG). The beta units differ and give individual hormones their specificity.

FSH and LH are produced during reproductive life in a rhythmic fashion (known as the menstrual cycle) and interact with ovarian hormones to produce regular ovulation (**Figure 5.2.**). The level of each of these hormones is dependant upon several mechanisms of feedback control. At the beginning of the menstrual cycle, FSH production is allowed to rise by the fall in oestrogen production from the previous waning corpus luteum (Johnson & Everitt 1984). As the FSH level rises many ovarian follicles respond (perhaps as many as 1000 per cycle) but only one, or rarely two, fully develop and go on to ovulate. The rest undergo atresia at an early stage. During the early follicular phase, secretion of ovarian steroids is at a relatively constant and low level. Then as the follicle develops, ovarian secretion of oestradiol increases slowly at first then more rapidly to reach a peak on the day before the LH peak. There is a rapid rise in the level of LH which leads to final maturation of the follicle and ovulation some 24-36 hours later.

At the time of the LH surge there is a sharp fall in plasma oestradiol level and the plasma progesterone begins to rise. The most important biochemical feature

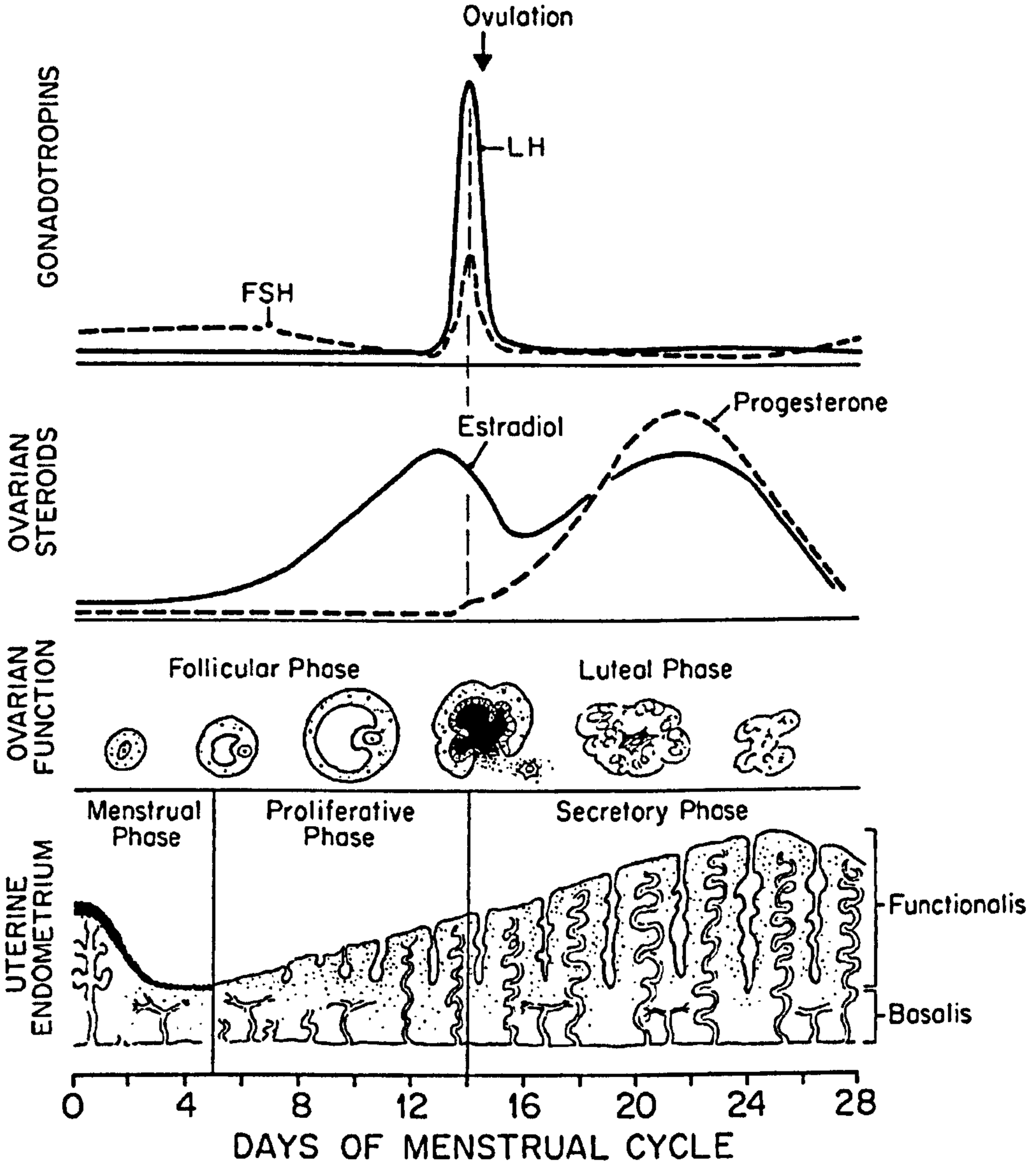


Figure 5.2.: Diagrammatic representation of changes in hormone levels, the ovary and the endometrium during the normal menstrual cycle.

of the luteal phase of the menstrual cycle is the secretion of progesterone, which reaches a maximum about 8 days after the LH peak. There is also a parallel but smaller increase in oestradiol levels. As the steroids increase, LH and FSH gradually decline, the FSH rising again at the end of the luteal phase to initiate the growth of the next follicle if fertilisation of the ovum and a pregnancy do not occur.

Women having regular menstrual cycles (frequency of 23-35 days, with no more than 2-3 days variation each month) have a greater than 95% chance that they are ovulating (Balen & Jacobs 1997). They will therefore experience the characteristic hormonal changes outlined above with a pre-ovulatory follicular phase of oestrogen dominance and a post-ovulatory luteal phase of progesterone dominance.

5.3. THE MENOPAUSE

Ovarian function starts to decline from as early as the 20th week of embryological life with oestrogen production falling to a critical level at the menopause. The problems of the "climacteric" have existed for centuries but according to a historical review it was not until 1816 that De Gardanne coined the term "La Menespausie" from the Greek *men* (month) and *pausis* (cessation) (Wilbush 1979). Aristotle (384-322BC) recognised that menstruation normally stopped around the age of 40 years but some women could continue with their periods until their 50th year. In the 17th century less than a third of women lived to experience the menopause. However, an increase in life expectancy in the twentieth century means that most women will spend a third of their adult life in the postmenopausal years.

The average age of the menopause is now generally accepted to be approximately 51 years, but some variation exists between different countries and geographical regions (Report of a WHO Scientific Group 1994). Population predictions

indicate that the 467 million postmenopausal women in the world in 1990 will have increased to 1200 million by 2030 (Hill 1996) (**Figure 5.3.**). Postmenopausal women make up over 15% of the population in industrialised countries with a growth rate of 1.5% predicted until the 2020's.

Serum FSH levels rise throughout the fifth decade of life and LH levels have been reported to increase as women approach the age of 50 (Lenton 1988). By 2-3 years after the last menstrual period, serum FSH levels have increased in value to 10-15 times higher than follicular phase levels in young women, and LH levels are about 3 times higher (Chakravarti 1976). A major change in the source and nature of circulating oestrogens occurs after the menopause. Quantitatively, the most important circulating oestrogen is oestrone (rather than oestradiol which is predominant premenopausally), with serum levels averaging about 100 pmol/L. Most of the oestrone is derived from the extraglandular conversion of adrenal androgen precursors, particularly androstenedione. Serum oestradiol levels after the menopause are generally less than 150pmol/L compared with a late premenopausal mean of 550 pmol/L.

The menopause is associated not only with a cessation of menstrual periods but also a wide range of symptomatic and pathophysiological changes. These include hot flushes, night sweats, loss of energy, ischaemic heart disease, osteoporosis and urogenital atrophy. The role of oestrogen deficiency in the pathogenesis urogenital complaints and the use of oestrogen replacement therapy for the treatment of these conditions is considered in detail in **Chapter six.**

A number of non-hormonal treatments have been used to treat menopausal problems with varying degrees of success. Galen (AD131-201) advised phlebotomy so that any "retained poisons" may be released and the use of purgatives and the application of leaches were popular in the sixteenth century. In 1777 John Leake

recommended "where the patient is delicate and subject to female weakness, night sweats or an habitual purging, with flushing in the face and a hectic fever: for such; ass's milk, jellies and raw eggs, with cooling fruits. At meals she may be indulged with half a pint of old, clear London porter, or a glass of Rhenish wine". In modern times treatments other than Hormone Replacement Therapy (HRT) often only serve to manage a particular symptom. Sedatives and tranquillisers have been prescribed for many women but unfortunately they only add to the lethargy and general loss of interest in life which may accompany the menopause. Clonidine (Clayden et al 1974, Lindsay & Hart 1999), propanolol (Alcoff et al 1981), methyldopa (Tulandi et al 1984) and naproxen (Haataja et al 1984) have all been used, mainly for the treatment of vasomotor symptoms, with conflicting results. Unfortunately, all are associated with side effects.

It has been recognised for some time that many hundreds of plants contain phytoestrogens, naturally occurring substances with some degree of oestrogenic activity (Bradbury & White 1954, Price & Fenwick 1985). Legumes are particularly rich in oestrogenic isoflavones while cereals contain oestrogenic lignans. Women living in Pacific rim nations eating a diet rich in soy experience less severe menopausal symptoms, whilst several chronic illnesses of menopausal women including breast cancer, colon cancer and cardiovascular disease have a much lower incidence than in Western countries (Morton & Griffiths 1998). Further work is required to establish the true benefit of phytoestrogens for women with established oestrogen deficiency.

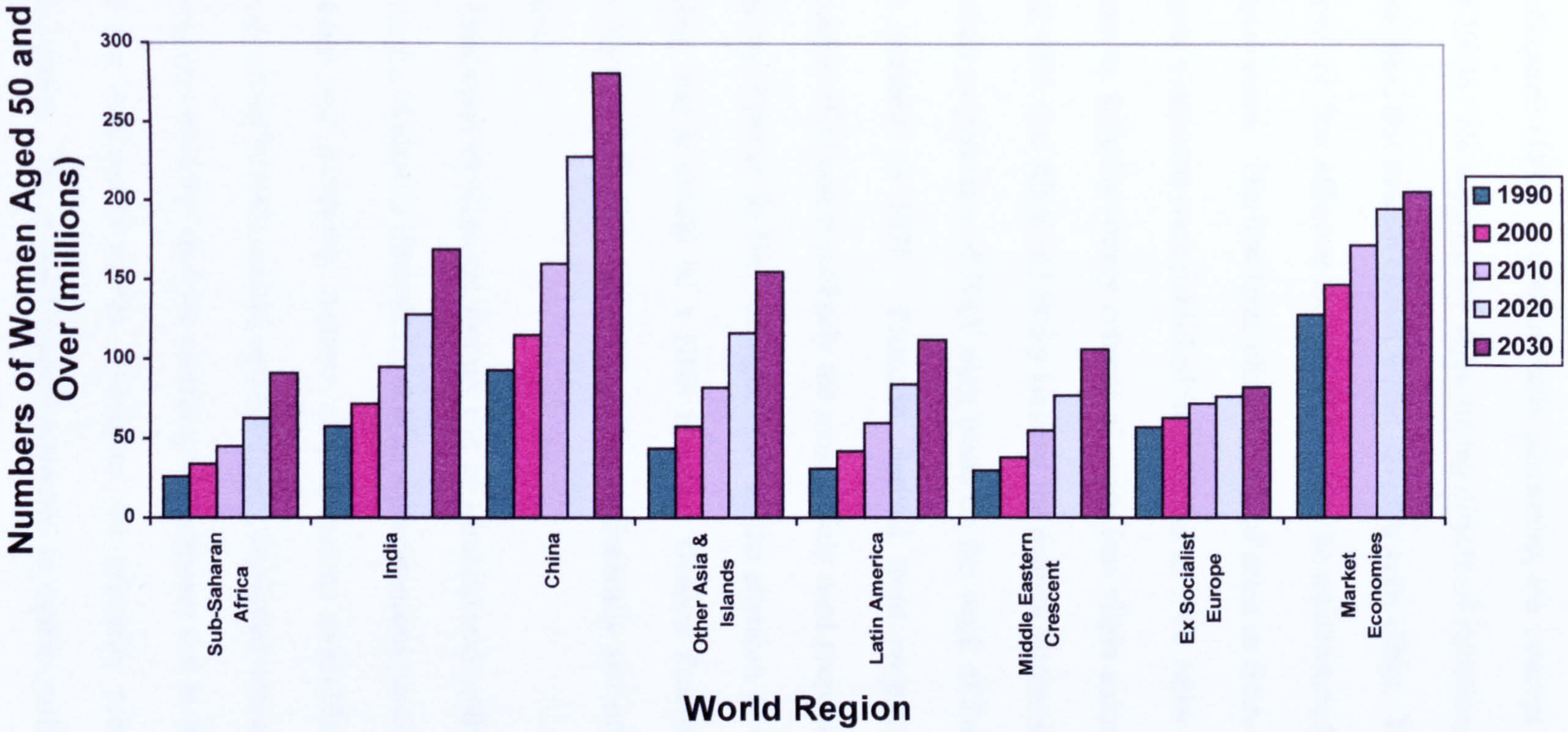


Figure 5.3.: Predicted population of postmenopausal women by region. Adapted from Hill (1996).

5.4. HORMONE REPLACEMENT THERAPY

Brown-Sequard (1889) is credited with pioneering the concept of HRT (O'Dowd & Philipp 1994). He reported the rejuvenating effects of injections of testicular extracts and postulated that ovarian extract would have the same effect. Two years later Murray developed the first effective form of HRT when he administered oral thyroid gland to treat myxoedema. The first three clinical trials of dried or fresh ovarian tissue to treat climacteric symptoms were published in 1896 and in 1912 Adler produced the changes of oestrus by injecting watery extracts of ovary into virgin animals. However, it was not until 1923 that Allen and Doisy isolated the ovarian hormone oestrogen. The first commercial preparations of HRT were based on the work of Zondek and Laquer and became available in 1926. Premarin, derived from pregnant mare's urine, was introduced in 1943 and is probably the most widely used preparation. The publication of *Feminine Forever* in 1966 brought HRT to the attention of the public with many demanding that it should be a NHS benefit. General Practitioners however were initially divided with some prescribing it enthusiastically and others being completely dismissive.

Oestrogen replacement therapy can be administered orally, transvaginally, as a subcutaneous implant or through the skin as a percutaneous patch, cream or gel. There are a large and increasing number of preparations available. The classes most commonly prescribed are natural, synthetic and conjugated equine. Of these, synthetic oestrogens are primarily used for contraceptive purposes and include ethinyl oestradiol. Natural and conjugated equine oestrogens are primarily prescribed for hormone supplementation. The primary equine oestrogen is equilin sulfate, this consisting of 33% of conjugated oestrogen.

The role of HRT and the advantages/disadvantages of different preparations for the treatment of osteoporosis, ischaemic heart disease and other conditions related to the menopause is beyond the scope of this review. However, the use of oestrogen and progesterone to treat urinary symptoms is outlined in **Chapter six.**

When serum concentrations of sex steroids are measured at short time intervals after administration or repeatedly during long term treatment it is clear that there are significant intra-individual and inter-individual variations (Kuhl 1990). Large fluctuations in oestradiol and oestrone level can be observed in an individual women from day to day or even from hour to hour. However, even with this in mind each type of oestrogen preparation has a characteristic pharmacokinetic profile (**Figure 5.4.**).

5.4.1. Oral oestrogen

The most commonly prescribed method of oestrogen administration is the oral route. Oestradiol is preferentially converted to oestrone in the gastrointestinal tract (Ryan & Engel 1953), and then the portal system transfers the absorbed steroid to the hepatic system. Typically, an oestrone : oestradiol ratio of 4 : 1 is achieved with oral therapy instead of the physiological ratio of 1 : 2 which occurs in premenopausal woman (Kuhl 1990). In the liver glucoronidation occurs so much of the oestrogen is metabolised and inactivated before the systemic circulation is reached – this is known as the "first pass" effect. As a consequence of these effects oral oestrogens need to be given at higher doses than parenteral oestrogens in order to achieve the same symptomatic relief (Studd & Barber 1992). Oral oestrogens are more potent than those given peripherally in elevating HDL cholesterol, thereby increasing the HDL/LDL ratio with the consequent beneficial implications for arterial and cardiovascular disease (Gordon et al 1977).

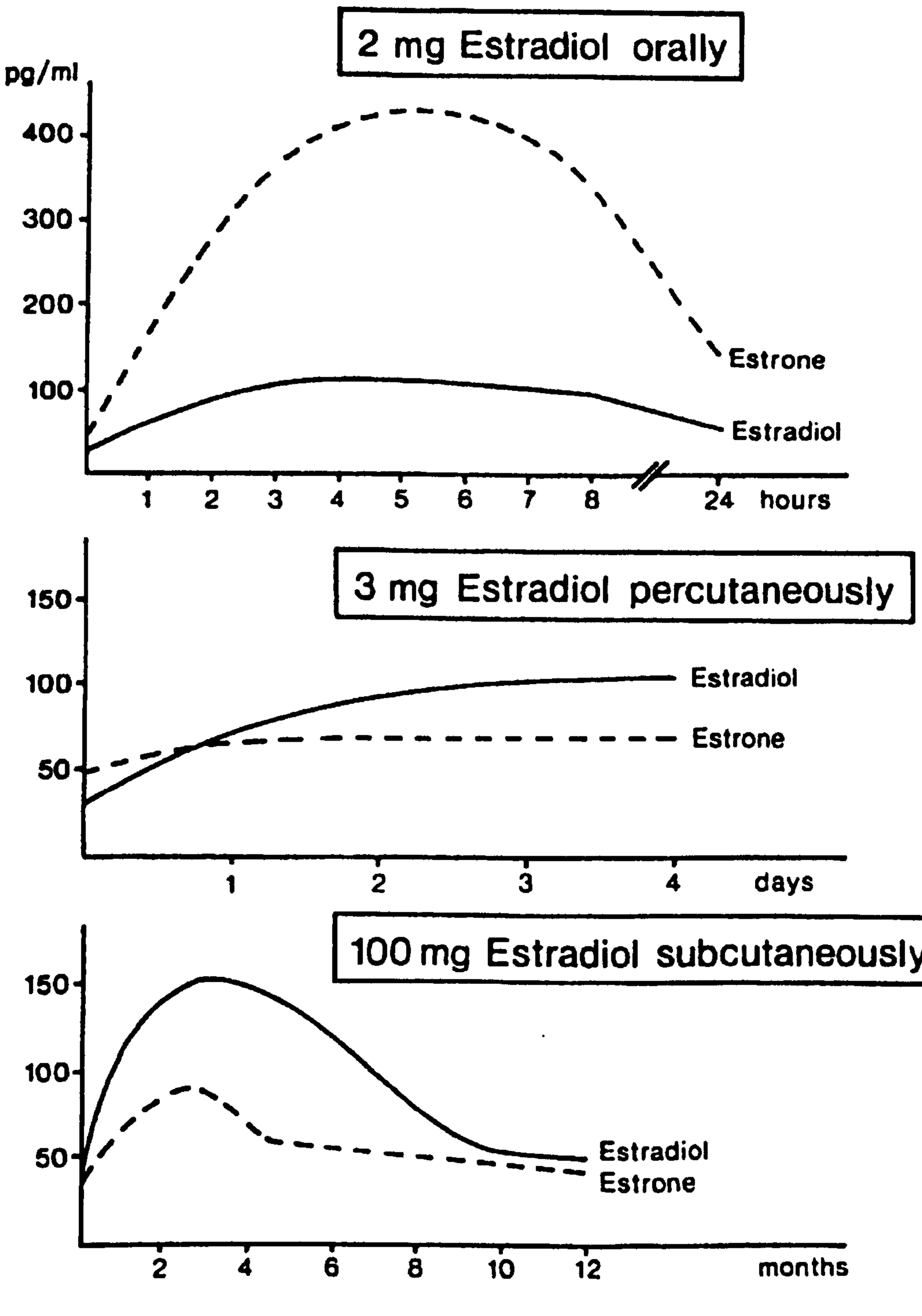


Figure 5.4.: Serum concentrations of oestradiol and oestrone after oral, percutaneous and subcutaneous administration of oestradiol, according to Kuhl (1990).

5.4.2. Transdermal and Percutaneous oestrogen

Skin patch delivery systems are usually called *transdermal* as the drug reservoir remains outside of the skin. A number of differently constructed skin patches have been studied but only two are widely used in clinical practice: reservoir and matrix patches. Reservoir patches contain oestradiol in a gel with a small amount of alcohol as a flux enhancer, enabling penetration through the skin barrier. Oestradiol is released continuously through a rate limiting membrane, when the system is applied directly to the skin, for approximately 3.5 days after which a new patch is applied (Kuhl 1990). Several combination oestrogen-progestogen patches are now available and are preferred by many women to the standard oestrogen patch-oral progestogen regime. Side effects are relatively minor, the most common adverse effect being skin irritation occurring in approximately 15-40% of women (Fraser & Wang 1998).

In the matrix patches, the oestrogen is evenly dispersed as a micronised suspension in a very thin adhesive matrix which is protected by a backing membrane of flexible translucent polyurethane film. The rate of drug delivery is controlled by diffusion through the skin, rather than by use of a rate limiting membrane as in the reservoir patches, and the absence of alcohol results in a very different pharmacokinetic behaviour. The rate of drug delivery from the system is relatively constant over the entire application period, resulting in less fluctuation of the plasma oestradiol level. New 7-day matrix patches are now available which tend to maintain a more constant blood hormone level than the traditional twice weekly patches.

In the past few years a number of percutaneous oestrogen gels have been developed which are now available in clinical practice. The gel is generally applied to the lower abdomen, arms or shoulder once daily. Unfortunately, absorption is

dependant upon the surface area of application and the intensity that it is rubbed in, leading to considerable inter-individual variation in the systemic levels achieved.

Oestrogen can also be given vaginally by tablet, cream or intravaginal ring but this method of delivery is often reserved for women with atrophic vaginitis. It may also have a role for prophylaxis against recurrent urinary tract infection in postmenopausal women and this is discussed further in **Chapter eight.**

5.4.3. Oestradiol implants

The use of subdermal implants has been advocated as a simple method of giving oestradiol for over 40 years. This form of HRT has the advantage that it is safe and simple to administer (usually every 6 months), has a long duration of action (approximately 5-12 months) and relatively stable absorption. In addition, first pass metabolism is avoided. From a research point of view, giving a woman an oestradiol implant rather than another form of HRT ensures compliance with treatment.

After insertion of an implant into the subcutaneous fat, oestradiol is released from this depot in small daily amounts. The release rate and resulting serum oestradiol levels depend primarily on the surface area of the implants (Studd & Magos 1987). The dimensions of the oestradiol implants commonly used in clinical practice are shown in **Table 5.1.**. The mean oestradiol levels generally reach their maximum within the first month and thereafter show a gradual decline. This trend was observed in the study reported in **Chapter 12** using 25mg oestradiol implants **(Table 12.5.)**.

DIMENSIONS	25MG	50MG	100MG
Length (mm)	6.0	2.8	5.6
Diameter (mm)	2.15	4.5	4.5
Surface area (mm^2)	48	71	112
Relative surface area (25mg=1.00)	1.00	1.48	2.33

Table 5.1.: Dimensions of commonly prescribed oestradiol implants (Personal communication, Organon Laboratories, Cambridge).

5.5. SAFETY OF UNOPPOSED OESTROGEN THERAPY

Many women feel that the main advantage of reaching the menopause is the cessation of menstruation. It is therefore not surprising that the resumption of vaginal bleeding associated with HRT is a major cause of dissatisfaction with this type of treatment. For postmenopausal women staring a 28 day sequential oestrogen and progestogen regimen the bleed is usually similar to or slightly less than previous menstruation, although 5% may not bleed at all (Sturdee 1998).

When HRT was introduced, unopposed oestrogen was commonly given to women with a uterus. In 1979 only 6% of HRT preparations prescribed in the UK contained a progestogen (Thom et al 1979). This in part was because of the favourable bleeding pattern associated with unopposed oestrogen therapy compared to HRT which also contains a progestogen; with oestrogen only HRT approximately 23% of women will not have any vaginal bleeding, 48% will have regular bleeds and only 29% will have an irregular cycle (Sturdee et al 1978).

The main problem with long term unopposed oestrogen is the significant risk that the patient will develop endometrial hyperplasia, a known precursor of endometrial carcinoma. Relatively little information is available on the background prevalence of endometrial hyperplasia, but some reports suggest it may be present in up to 5% of postmenopausal women who do not use HRT (Archer et al 1991). Unopposed oestrogen therapy is associated with an incidence of hyperplasia of 15-50%, depending upon the dose and duration of therapy used, and an increased risk of endometrial cancer up to 6 fold (Paterson et al 1980, Schiff et al 1982, Whitehead 1987). A recent review (Herrington & Weiss 1993) and meta-analysis (Grady et al 1995) have been undertaken to evaluate the risk of endometrial carcinoma with HRT. Herrington assessed 18 studies and found that unopposed oestrogen therapy for greater than 5 years increased the risk

of endometrial cancer by a factor ranging between 1.8-36. Grady identified 30 controlled studies and found that unopposed oestrogen elevated the relative risk 2.3 fold, with prolonged therapy of greater than 10 years increasing the relative risk to 9.5. Six studies reported that the relative risk of developing endometrial carcinoma when oestrogen alone was used for six months or less was negligible (range 0.6-1.4).

When deciding upon a suitable treatment interval for the placebo controlled trial reported in **Chapter 12** a balance needed to be achieved between giving oestrogen for an adequate period of time without jeopardising patient safety. In view of the reported data a treatment period of six months was felt to be ethically acceptable, providing the endometrium was assessed at the start of the trial. It is unknown whether six months is an adequate period of time to observe maximal therapeutic benefit of oestrogen therapy for urinary symptoms, but if no benefit had been achieved after this period then few women would find HRT an acceptable way of managing their urinary complaint. The action of progestogens counteracts the proliferative effect of oestrogens on the endometrium and the concurrent use of a progestogen has been shown to significantly reduce the risk of endometrial hyperplasia. When added for seven days the risk of endometrial hyperplasia is reduced to 4%, with 10 days of progestogen 2% and with 12 days 0% if given at an adequate daily dosage (Sturdee et al 1978). It was therefore decided to treat women developing vaginal bleeding during the study with an oral progestogen.

During the study reported in **Chapter 12** those women randomised to oestrogen received unopposed therapy, regardless of whether they had a uterus or not. This was done for the following reasons:

1) Progestogens may adversely effect lower urinary tract function, as outlined in **Chapter six** and investigated further in **Chapter nine.** Progestogens are associated with irritative bladder symptoms (Cutner et al 1993) and incontinent women taking HRT have been shown to loose more urine during the progestogenic phase of their treatment (Benness et al 1991). Therefore, the concurrent use of a progestogen introduces a confounding variable into the analysis which would make interpretation of the efficacy of oestrogen problematic, particularly in view of the unknown magnitude of the progestogenic effect.

2) If a progestogen had been administered on a monthly basis those women being treated with oestrogen would have had a withdrawal bleed, rapidly unblinding the trial. An alternative to this would have been only to include hysterectomised women, but it was felt that sufficient numbers would not be recruited from a single centre over the time span of this thesis to produce a study with sufficient statistical power. Therefore, it was decided to treat the women with unopposed 25mg oestradiol implants. This relatively low dose implant was chosen to try and minimise the effects of on the endometrium while providing an adequate therapeutic dose of oestradiol.

5.5.1. Endometrial assessment

Transvaginal ultrasonography is now a widely used technique for the evaluation of the endometrium as it is less invasive than performing a Dilatation and Curettage (D & C) or taking an endometrial pipelle (Lindgren et al 1999). In *untreated* postmenopausal women an endometrial thickness <4mm has rarely been found to be associated with significant pathology. Using this cut off level an endometrial abnormality is found in

less than 1% of asymptomatic postmenopausal women. This technique was therefore used for the baseline assessment of the endometrium in the study presented in **Chapter 12.** When HRT is given the endometrial thickness frequently increases and a cut off level of 4mm is therefore no longer appropriate as it may lead to unnecessary biopsies being performed. In a study of 564 climacteric women taking HRT Lindgren and colleagues (1999) found that 53% of the women had an endometrial thickness of >4mm on ultrasound.

In those patients with a thickened endometrium or unexplained vaginal bleeding endometrial sampling is necessary so that histological evaluation can take place. An accepted alternative to the traditional D & C is the use of a Pipelle sampler (Cornier 1984). This device has a flexible polypropylene outer sheath with an external diameter of 3.1mm which is gently pushed through the cervix to the uterine fundus. An inner piston is withdrawn to the end of the sheath, so applying negative pressure, and the Pipelle rotated with a gentle "to and fro" movement. The device has been found to produce an adequate sample in both premenopausal and postmenopausal women with 95-100% of carcinomas being detected (Fothergill & Brown 1992, Batool et al 1994). As with all blind sampling techniques it is important not to be reassured by non-specific reports arising from an inadequate specimen. In this situation the options are to either repeat the Pipelle sampling or perform a formal D & C. If scanning is employed, one reduces the likelihood of missing endometrial pathology such as polyps. Furthermore by having a cut off of an endometrial thickness of 4mm in untreated women, many potentially inadequate samples are avoided and the sensitivity of the biopsy technique increases (Goldchmit et al 1993). In summary, transvaginal ultrasound was performed to assess the endometrium in this thesis, with an endometrial biopsy being taken using a Pipelle sampler or D & C when necessary.

CHAPTER 6

OESTROGEN AND THE FEMALE LOWER URINARY TRACT

6.1. INTRODUCTION

Oestrogen has an important role in the function of the female lower urinary tract throughout adult life. Sex steroid receptors have been located in areas of the brain involved in the initiation and control of micturition as well as tissues of the bladder, urethra and pelvic floor. Fluctuations in the circulating level of oestrogen and progesterone are thought to be responsible for changes in the prevalence of urinary symptoms and the results of urodynamic investigations which occur during the menstrual cycle and in pregnancy. In addition, there is epidemiological evidence from several studies implicating the menopause and subsequent oestrogen deficiency in the pathogenesis of a number of urinary complaints including incontinence, the "urge syndrome" and recurrent urinary tract infections. Oestrogen has been used widely to treat urinary symptoms in postmenopausal women but there are relatively few randomised studies which makes it difficult to draw accurate conclusions about its true efficacy. The aim of this chapter is therefore to critically review the role of oestrogen in the pathogenesis and treatment of lower urinary tract dysfunction.

6.2. THE EFFECT OF OESTROGEN ON THE FEMALE LOWER URINARY TRACT

For a woman to remain continent urethral pressure must exceed the intravesical pressure at all times except during micturition (Abrams et al 1990). As described in **Chapter two,** this effect is maintained by the complex interaction of neurological and muscular factors in conjunction with a variety of different pelvic fascial supports, particularly of the urethra. Oestrogen influences the female lower urinary tract and continence mechanism in a number of important ways. Sex steroids appear to be involved in the neuronal control of the continence mechanism and evidence is emerging that hormones

may have a direct (non-genomic) effect on detrusor smooth muscle function. In addition, the functional layers of the urethra which help to maintain a positive urethral closure pressure (epithelium, vasculature, muscle and connective tissue) all appear to be target sites for oestrogens.

6.2.1. Neuronal control

During a woman's reproductive life gonadal steroids interact with neurotransmitters and neuropeptides at the hypothalamic level modifying the synthesis and release of gonadotrophin-releasing hormone (GnRH). It is now clear that oestrogens are also of critical importance in a number of other cerebral functions including pain control, thermoregulation, mechanisms such as hunger and thirst, and psychological well being. Oestrogen receptors are found throughout the brain cortex, limbic system, hippocampus and cerebellum (Maggi & Perez 1985, Smith 1993). In these regions oestrogens are able to alter the synthesis, release and metabolism of neurotransmitters such as dopamine, acetylcholine, serotonin and melatonin. This may explain why oestrogens can improve cognitive function and enhance mood in the perimenopausal and postmenopausal period (Schneider et al 1977, Sherwin 1988, Ditkoff et al 1991, Best et al 1992).

Recent animal studies have shown that androgen receptors are present in the pontine micturition centre (Blok & Holstege 1998). They are also found in the preoptic area of the hypothalamus, an area of the forebrain which may play an important role in the initiation of micturition. Further work is required to establish if the exact type and distribution of sex steroid receptors in the human micturition pathways and their importance in the control of the continence mechanism.

6.2.2. Bladder

Oestrogen receptors are not found in the transitional epithelium of the bladder apart from in areas of the trigone which have undergone squamous metaplasia (Wilson et al 1984, Wolf et al 1991, Blakeman et al 1996a). However, oestrogen has a direct (non-genomic) effect on detrusor function which is thought to be secondary to modifications in muscarinic receptors (Shapiro 1986, Batra & Anderson 1989, Elliott & Castleden 1994) and inhibition of movement of extracellular calcium ions into muscle cells (Elliott et al 1992a). Animal studies have shown that oophorectomy alters the pressure flow characteristics of micturition in the female rat (Diep & Constantinou 1999). This effect may only be partly reversed by oestrogen supplementation and is possibly age dependent. It is at present unknown if similar effects occur in humans. Oestradiol reduces the amplitude and frequency of spontaneous rhythmic contractions, which have been associated with detrusor instability (Shenfield et al 1998), and *in vivo* oestrogen pre-treatment reduces the contractile response of isolated rat detrusor muscle (Elliott et al 1992b). There is also some evidence to suggest that in women the sensory threshold of the bladder may be raised by oestrogen supplementation, allowing patients to hold more urine before they need to void (Fantl et al 1988).

6.2.3. Urethra and pelvic floor

The female lower urinary and genital tracts have a common embryological origin, both arising from the primitive urogenital sinus (**Chapter two**). It is therefore not surprising that oestrogen receptors are consistently expressed in the squamous epithelium of the bladder trigone, urethra and pubococcygeus muscle of the pelvic floor as well as the vagina (Iosif et al 1981, Ingelman-Sundberg et al 1981, Smith 1993, Blakeman et al 1996a). The "classical" oestrogen receptor (ERα) was discovered in 1958 (Enmark &

Gustafsson 1999). For many years it was considered that only one type of oestrogen receptor existed. However, in 1996 a second oestrogen receptor was isolated, now recognised as oestrogen receptor β (ER β)(Kuiper et al 1996). This finding suggests that the mechanisms behind the effects of oestrogen are far more complicated than previously assumed, with possible different physiological roles for each oestrogen receptor subtype. At present there are only very limited published data on the different types of oestrogen receptor in the urogenital tract (Chen et al 1999). Preliminary work suggests that while ERα is consistently found in both the vaginal wall and uterosacral ligaments, ERβ expression is more variable and may be dependant upon menopausal status. Further work is awaited with interest.

A number of authors have shown that oestrogen increases urethral closure pressure and improves pressure transmission to the proximal urethra, effects which probably occur by a combination of different mechanisms (Rud 1980, Hilton & Stanton 1983b, Bhatia et al 1989, Karram et al 1989). In response to oestrogen there is an increase in cell cycle activity and an improved "maturation index" of the urethral epithelium (Samsioe et al 1985a, Bergman et al 1990, Blakeman et al 1996b) with similar changes also occurring in the in the vagina of postmenopausal women (Smith 1976, Semmens et al 1985). Alterations in urinary cytology during the menstrual cycle are comparable with those seen in vaginal cytology (McCallin et al 1950), changes which can also be identified in the urinary sediment following treatment with oestrogens (Soloman et al 1958).

The vasodilatory effects of oestrogens which occur in the systemic and cerebral circulations also take place in the female urethra (Ganger et al 1991, Penotti et al 1997, Jackson & Vyas 1998). Versi and Cardozo (1986) have shown that vascular pulsations seen on urethral pressure profilometry (UPP), secondary to blood flow in the urethral

submucosa and urethral sphincter, increase in size in response to oestrogen. Attempts have been made to quantify changes in urethral blood flow in response to oestrogen therapy using Doppler ultrasound (Jackson et al 1997). Unfortunately, difficulties in imaging the same vessel repeatedly and natural variation in blood flow through pelvic vessels limit the reproducibility of the technique.

Oestrogen sensitises the alpha-adrenergic receptors in the urethral sphincter and therefore may contribute to its muscular tone (Screiter et al 1976).

Connective tissue metabolism and production of collagen is stimulated by oestrogens, therefore possibly reversing the reduction in total vaginal and periurethral collagen which is associated with genuine stress incontinence and genitourinary prolapse (Jackson et al 1996, James et al 1999a, James et al 1999b). Evidence is emerging that these conditions are both associated with a systemic change in collagenase activity (Kushner et al 1999). However, studies are still required to determine if prophylactic treatment with hormone replacement therapy or other medications will be sufficient to prevent their development, particularly in view of the fact that both have a multifactorial aetiology.

The oestrogen status of the patient can therefore have a significant effect on urethral pressure (Rud 1980), and this may be particularly important when there is already a degree of weakness.

6.3. THE EFFECT OF PROGESTOGENS ON THE FEMALE LOWER URINARY TRACT

Progesterone receptors are expressed inconsistently in the lower urinary tract and may be dependent on the oestrogen status of the woman (Batra & Iosif 1987, Blakeman et al 1996a). Unfortunately, there is very little data on the physiological effects of

progesterone on the lower urinary tract outside pregnancy but in general progestogens have an adverse effect on the bladder and urethra. The physiological hydroureter of pregnancy is thought to arise from a combination of both mechanical and hormonal factors. The relative contribution of each is uncertain but progesterone does cause some degree of relaxation of ureteric smooth muscle both in-vitro and in-vivo (Swift & Ostergard 1993). Urodynamic studies performed in pregnancy have shown a higher prevalence of detrusor instability antenatally than that found postpartum (Cutner 1993). The exact mechanism for this is unclear, but the high physiological levels of progesterone found in pregnancy are thought to be an important aetiological factor. Animal studies have suggested that progesterone may cause smooth muscle relaxation, induce Beta-adrenergic receptor formation, antagonise the inhibitory effect of oestradiol on rat detrusor muscle contraction and increase bladder sensitivity to contraction evoking bethanacol (Ekstrom et al 1993, Elliott & Castleden 1994).

Clinically progestogens are associated with an increase in irritative bladder symptoms. Cutner and colleagues (1993) studied nine women with premature ovarian failure who were undergoing in-vitro fertilisation (IVF) and having their artificial menstrual cycles manipulated with physiological levels of oestrogen and high does of progesterone. Urinary symptom questionnaires and urodynamic investigations were completed during the two phases of treatment (oestrogen alone and oestrogen with progesterone). The authors found that the number of voids per 24 hours was significantly greater in the progesterone phase as was the pressure at the end of filling cystometry. Burton (1992) questioned 217 women with premature ovarian failure on continuous oestrogen and cyclical progesterone therapy. They found an increase in the symptoms of urgency during the progesterone phase of the cycle but no change in the incidence of stress incontinence or urge incontinence. However, using pad testing

Benness (1991) did find an increase in urinary loss during the progesterone phase of treatment in 14 postmenopausal women with urinary incontinence who were taking HRT. Despite these findings, progestogens do not appear to alter the urethral pressure profile significantly (Raz et al 1973, Rud 1980).

6.4. THE EFFECT OF ANDROGENS ON THE FEMALE LOWER URINARY TRACT

Androgen receptors are found both in the female bladder and urethra, but their role is at present unclear (Blakeman et al 1997). The use of androgens to treat urinary symptoms in women is limited by their masculinising side effects and is therefore not considered further.

6.5. EVIDENCE OF AN ASSOCIATION BETWEEN SEX STEROID LEVELS AND URINARY SYMPTOMS

6.5.1. Menstrual cycle

The characteristic hormonal changes occurring during the normal menstrual cycle are outlined in **Chapter five.** It has long been recognised that women may notice a change in their urinary symptoms during the menstrual cycle which seem to coincide with the cyclical variations in the level of sex steroids. In particular some women report an increase in irritative bladder symptoms and a deterioration in their ability to maintain continence just prior to menstruation. It is thought that this may be secondary to an increase in circulating progesterone levels which occurs in the luteal phase of the normal menstrual cycle. However, the proportion of women affected by such fluctuations in hormone levels has not been prospectively evaluated. This area is therefore investigated further in the study in **Chapter nine.**

There are a limited number of reports relating to urodynamic changes during the menstrual cycle. Van Geelen (1981) serially measured the urethral pressure profile (UPP) of 27 nulliparous women with normal ovulatory cycles. No significant changes were found in the pressure measurements but there was an increase in the functional urethral length midcycle and early in the luteal phase. The data suggested a causal relationship between changes in serum oestradiol and alterations in urethral length. As with other studies (Raz et al 1973, Rud 1980) the authors could find no relationship between progesterone levels and the UPP parameters.

Information regarding the effect of the menstrual cycle on cystometry is very limited. In a case report Lewis and Warrell (1989) described an 18 year old women who noticed deterioration in her urinary symptoms during menstruation. Cystometry performed mid-cycle failed to show any significant abnormality. However, when this was repeated during menstruation the patient was found to have detrusor instability. The authors suggested that the cause for this was cyclical prostaglandin synthesis and this is supported by the fact that the patient's symptoms completely resolved when she was given the prostaglandin synthesis inhibitor mefenamic acid. Sorenson and colleagues (Sorensen et al 1988) performed urodynamic investigations on 10 healthy women three times during the menstrual cycle. No significant changes attributable to the menstrual hormonal changes were observed in the profilometry data, cystometric parameters or in the pressure-flow studies. There were no cases of detrusor instability but this is perhaps not surprising as all the women were well and asymptomatic. In contrast Shimonovitz (1997) performed a retrospective analysis of cystometry results from a urodynamic database. The study group comprised 57 women with regular menstrual cycles who had their investigations performed on a single occasion. Abnormal urodynamic diagnoses including detrusor instability were made more

frequently in the follicular phase and significantly more normal results were found in the women who felt that their symptoms were influenced by the menstrual cycle compared to those who felt there was no association. However, the retrospective nature of this study and small number of patients investigated in each phase of the menstrual cycle make it difficult to make any definite conclusions. In view of the limitations of these studies the impact of the menstrual cycle on the results of urodynamic investigation in symptomatic women is investigated further in **Chapter nine.**

6.5.2. Pregnancy

Many women complain of urinary symptoms during pregnancy which are only in part due to an increase in urine output and pressure effects from the gravid uterus (Stanton et al 1980, Cutner 1993, Chaliha et al 1998). As described earlier, progesterone levels are increased in pregnancy and this may account for the physiological hydroureter and increased prevalence of detrusor instability (Cutner et al 1992).

6.5.3. Menopause and oestrogen deficiency

Hormonal changes occurring at the time of the menopause have an impact on all oestrogen sensitive tissues and the female urogenital tract is no exception. Oestrogen deficiency, particularly when prolonged, is associated with a wide range of urinary symptoms including frequency, nocturia, incontinence, urinary tract infections and the "urge syndrome." These may co-exist with vaginal atrophy and symptoms of dryness, itching, burning and dyspareunia. Urinary symptoms secondary to oestrogen deficiency may only develop many years after the menopause and, therefore, may be under-reported in epidemiological studies by both patient and doctor. Iosif and Bekassy (1984) studied 902 Swedish women aged 61 years and found the prevalence of lower

urinary tract disorders was high with 49% of women having some symptoms. Of the 29% of women with incontinence, 70% related the onset of their urinary leakage to the time of their final menstrual period. In a survey of 2045 British women aged between 55 and 85 years, Barlow and colleagues (1997) showed that urogenital symptoms had affected 49% of postmenopausal women at some time and 11% were currently troubled by individual symptoms. At least two thirds of women did not relate their vaginal or urinary complaint to the menopause which may have occurred many years previously. Urinary tract symptoms are certainly common following the menopause with one in five women attending a menopause clinic complaining of severe urgency, and nearly 50% stress incontinence (Cardozo et al 1987).

The prevalence of postmenopausal incontinence in the community is thought to be between 16 and 29% (Vetter et al 1981, Jolleys 1988, Rekers 1992). While there are clearly a number of important factors in the pathogenesis of urinary incontinence there is conflicting evidence regarding the role of the menopause. Thomas (1980) (**Figure 6.1.**) and Jolleys (1988) (**Figure 6.2**) found the peak prevalence of urinary incontinence in community dwelling women to occur in the perimenopausal age group. Urge incontinence in particular is found more commonly after the menopause (Kondo et al 1990) with the prevalence appearing to rise in line with increasing years of oestrogen deficiency (**Figure 6.3.**). However, most studies show that many women develop incontinence at least 10 years before their last period, with Jolleys (1988) and Burgio (1991) finding that significantly more premenopausal women than postmenopausal women were affected. The prevalence of stress incontinence in the community also starts to fall following the menopause, particularly in age groups which are most likely to be affected by relative oestrogen deficiency, and the increase in urge incontinence and detrusor instability in elderly women may simply be an effect of the ageing process.

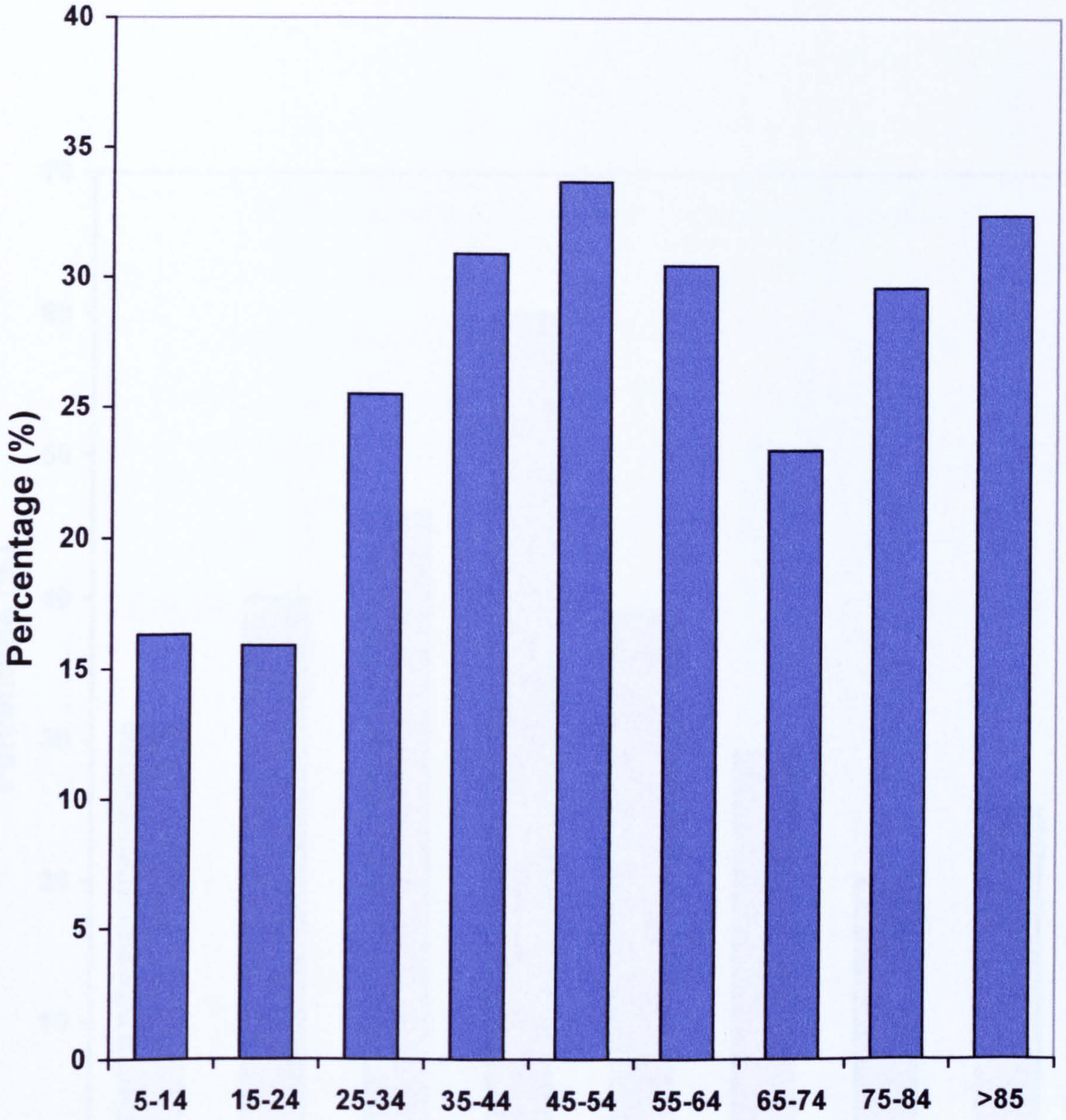


Figure 6.1.: Changing prevalence of occasional or regular incontinence with age among 9323 women responding to a postal questionnaire. Adapted from Thomas (1980).

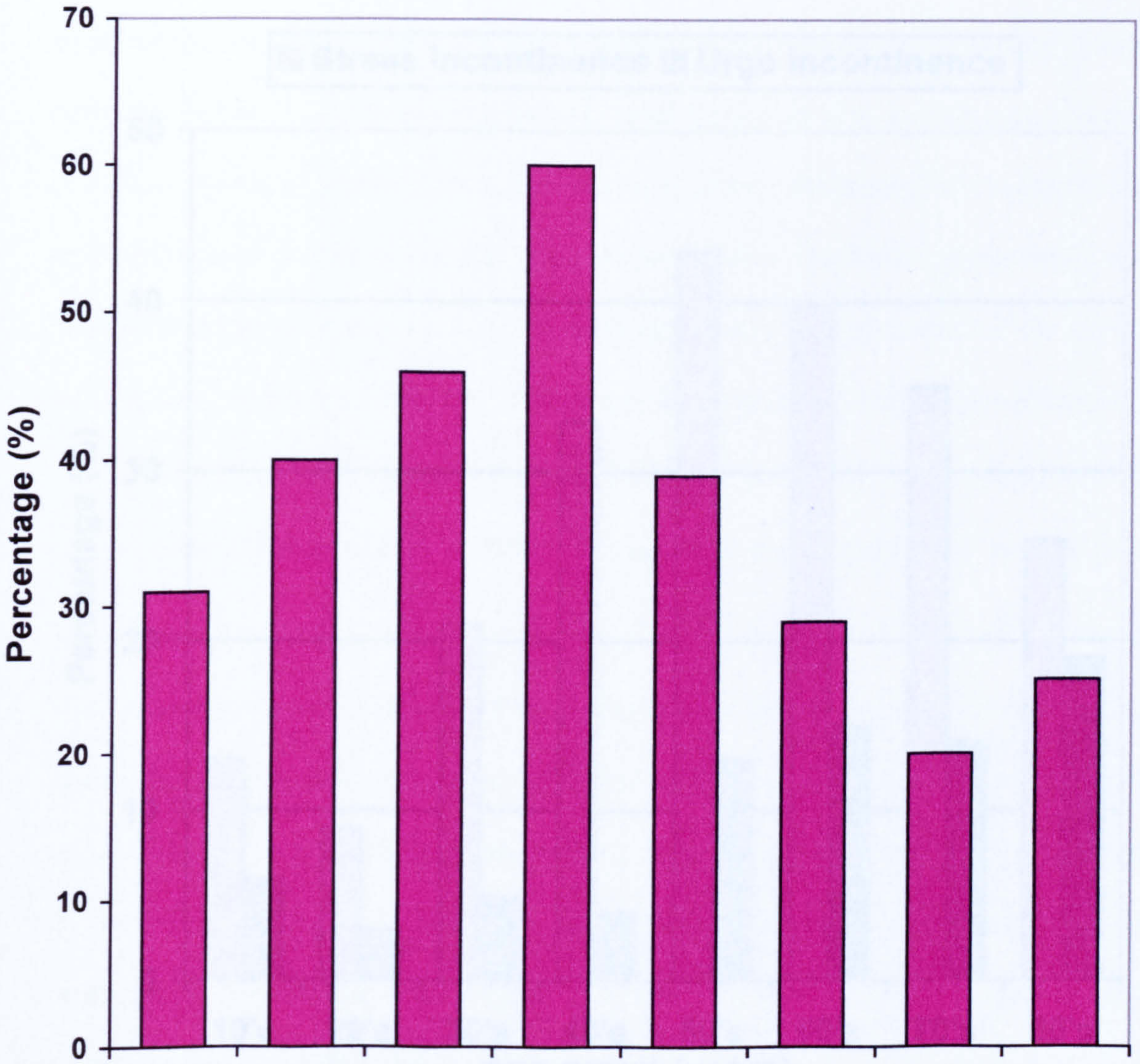


Figure 6.2.: Changing prevalence of incontinence with age among 937 women registered with a rural general practice. Adapted from Jolleys (1988).

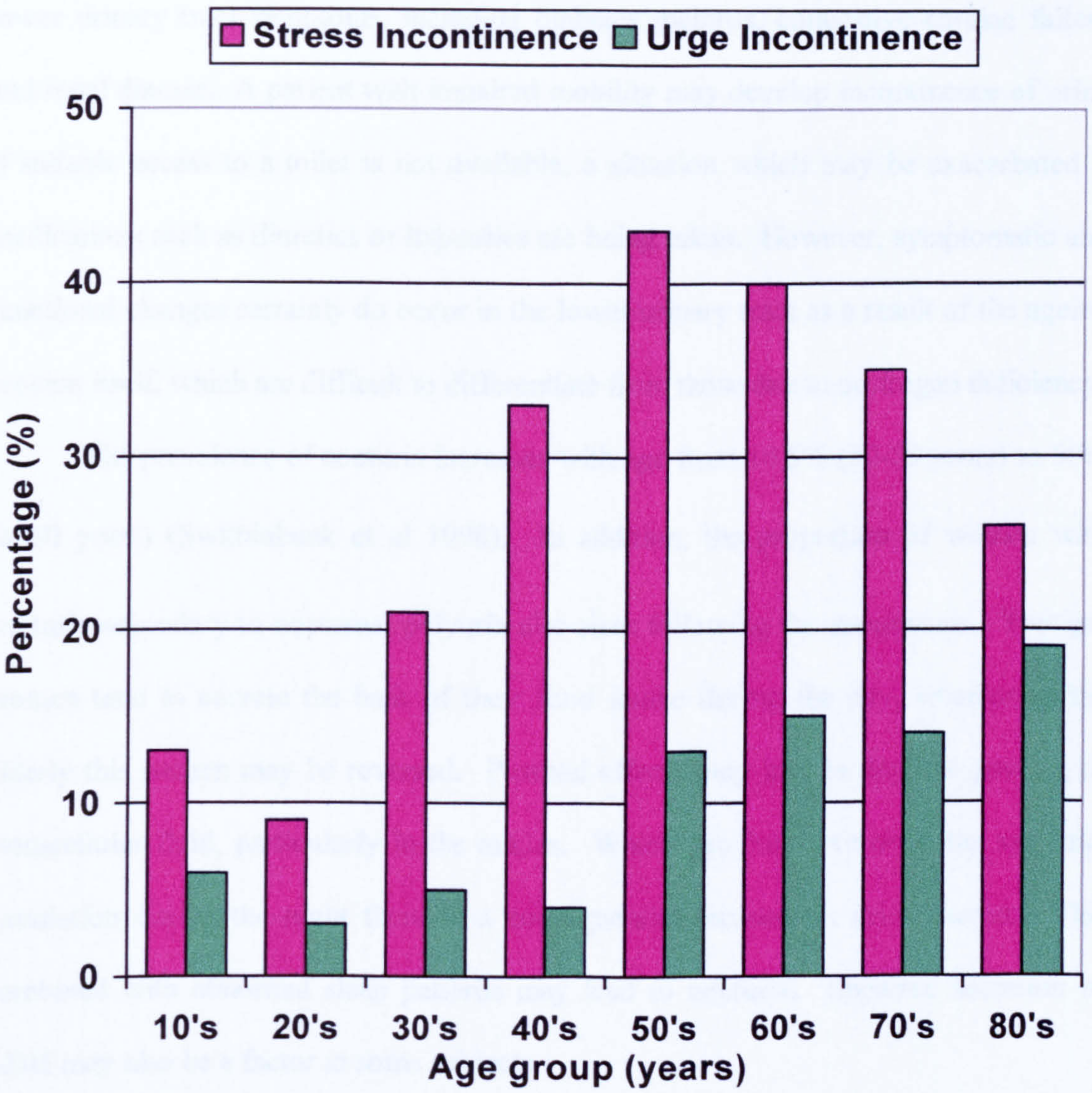


Figure 6.3.: Changes in the prevalence of stress and urge incontinence with age among 1100 Japanese women. Adapted from Kondo (1990).

6.6. THE EFFECT OF AGEING

Many women consider the development of urinary symptoms as they get older to be a normal phenomenon rather than the manifestation of a disease (Svanberg 1977). In a study of Gjorup and colleagues (1987), over 50% of women aged more than 75 years thought their symptoms were normal for elderly people. The ageing population are at risk of a number of systemic illnesses and transient problems which may present with lower urinary tract symptoms, including diabetes mellitus, congestive cardiac failure and renal disease. A patient with impaired mobility may develop incontinence of urine if suitable access to a toilet is not available, a situation which may be exacerbated if medications such as diuretics or hypnotics are being taken. However, symptomatic and functional changes certainly do occur in the lower urinary tract as a result of the ageing process itself, which are difficult to differentiate from those due to oestrogen deficiency.

The prevalence of nocturia increases with age from 10.5% (50-59 years) to 50% (≥ 80 years) (Swithinbank et al 1998). In addition, the proportion of women with nocturia secondary to nocturnal polyuria also rises following the menopause. Younger women tend to excrete the bulk of their fluid intake during the day, whereas in the elderly this pattern may be reversed. Postural effects may lead to daytime pooling of extracellular fluid, particularly in the ankles. When this fluid returns to the systemic circulation during the night there is a consequential increase in urine output. This combined with abnormal sleep patterns may lead to nocturia. Impaired secretion of ADH may also be a factor in some subjects.

Urodynamic studies have shown that the bladder becomes less efficient with age (Rud et al 1980, Malone-Lee & Waheda 1993, Collas & Malone-Lee 1996). Elderly women have a reduced urine flow rate, increased urinary residual, higher first sensation to void and increased bladder capacity, although the later may fall in the eight and ninth

decades. Detrusor pressures at urethral opening and closure during voiding fall in absolute terms as women become older (Wagg et al 1996). Histologically there is an age-related increase in fibrosis in the bladder neck (Brocklehurst 1972) and collagen content of the female bladder (Susset et al 1978). In a post-mortem study of the female urethral sphincter, Perucchini and colleagues (Perucchini et al 1997) demonstrated a reduction in the number of striated muscle fibres and their density with increasing age, but the size of individual fibres remained unchanged. However, the number and diameter of the fibres in the muscles of the pelvic floor does appear to decrease with age (Kolbl et al 1989) although neuronal damage secondary to childbirth may be a confounding factor (Smith et al 1989, Allen & Warrell 1992).

6.7. OESTROGEN FOR THE TREATMENT OF URINARY SYMPTOMS

If oestrogen does significantly affect the genitourinary tract then it is a reasonable assumption that it will be of some therapeutic benefit in postmenopausal women with urinary complaints. Salmon (1941) was the first to report the successful use of oestrogens to treat urinary incontinence over 50 years ago. Indeed, there are a number of reasons why oestrogens may be useful for the treatment of lower urinary tract dysfunction (**Table 6.1.**). It is now well recognised that there is a poor correlation between a woman's symptoms and the subsequent diagnosis following appropriate investigation (Jarvis et al 1980). Unfortunately, initial trials took place before the widespread introduction of urodynamic studies and therefore almost certainly included women with a number of different pathologies. Lack of objective outcome measures also limit their interpretation.

Increased urethral closure pressure
• Increased urethral cell maturation
• Increased urethral blood flow
• Increased alpha-adrenergic receptor sensitivity in urethral smooth muscle
Improved abdominal pressure transmission to proximal urethra
Stimulation of periurethral collagen production
Improved neuronal control of micturition
Increased sensory threshold of the bladder
Improved mood and quality of life
Reduced incidence of urinary tract infection

Table 6.1.: Mechanisms by which oestrogen may improve urinary incontinence.

6.7.1. Oestrogens for stress incontinence

There are a large number of reported studies of oestrogen for the treatment of urinary stress incontinence but most have to be interpreted with caution because they are observational and not-randomised, blinded or controlled. Comparison of the different reports is also difficult because a number of different types of oestrogen have been used with varying doses, routes of administration and durations of treatment. The concurrent use of progestogens, to prevent endometrial hyperplasia in those women with a uterus, probably also influences success rates. A summary of the controlled trials comparing oestrogen with a placebo is shown in **Table 6.2.**.

A meta-analysis from the Hormones and Urogenital Therapy (HUT) committee has helped to clarify the situation (Fantl et al 1994). Of 166 articles identified which were published in English between 1969-1992, only 6 were categorised as randomised trials and 17 uncontrolled series. Subjectively, oestrogen was found to produce a significant improvement for all patients and those with genuine stress incontinence, but this may have been because oestrogens improve feelings of wellbeing and quality of life. Consistent with other therapies for incontinence there was also a marked improvement in the placebo arm ranging from 10-56%. Analysis of objective parameters failed to show any reduction in the volume of urine lost compared to pre-treatment levels. Maximum urethral closure pressure did increase significantly, but this result was influenced by only one study showing a large effect. However, even this meta-analysis may have some serious methodological flaws. For example, a study by Judge (1969) was included and described as a randomised trial. Allocation to treatment in this report was based upon place of residence (in one of two different nursing homes) and may therefore be open to significant bias. In addition, the study population was not ideal for assessing if oestrogen is effective for the treatment of incontinence secondary

STUDY	NUMBER OF WOMEN	SYMPTOMS	URODYNAMICS	TYPE OF OESTROGEN	DURATION OF THERAPY	RESULTS
Samsioe 1985b	34	SI or UI or Mixed	_	Oral oestriol	3 months	No improvement in SI. UI and mixed improved.
Wilson 1987	36	SI	GSI	Oral oestrone sulphate	3 months	No significant subjective or objective improvement.
Sacco 1990	34	SI	GSI	Vaginal oestriol	3 months	Subjective improvement in SI and increased MUCP.
Cardozo 1990	46	SI	GSI	Oestradiol implant	3 months	No subjective improvement. Decreased bladder neck descent.
Fiodart 1991	109	Not specified	_	Vaginal oestriol	6 months	Improvement no better than with placebo.
Molander 1991	40	Not specified	_	Oral oestriol	10 weeks	Subjective improvement.
Fantl 1996	83	"Involuntary loss of urine"	45% GSI	Conjugated equine oestrogen + cyclical medroxyprogesterone	3 months	No subjective or objective improvement.
Jackson 1999	67	SI	GSI +/- DI	Oral oestradiol	6 months	No subjective or objective improvement.

Table 6.2.: Randomised trials comparing oestrogen therapy with placebo for undiagnosed incontinence or stress incontinence.
SI = Stress incontinence, UI = Urge incontinence, GSI = Genuine stress incontinence

to oestrogen deficiency. All the women included had neurological disease and 12 patients were described as being confused. The other problem with meta-analysis is that only studies with a positive outcome are likely to be reviewed, as research which does not show a treatment to be of benefit is less likely to be published.

In a further review of the literature, Sultana and Walters (1995) examined 8 controlled and 14 uncontrolled prospective trials and included all types of oestrogen treatment. They also found that oestrogen was of no benefit for stress incontinence but may be useful for the often associated symptoms of urgency and frequency.

Two further studies using oral oestrogen, which were not included in the HUT meta-analysis, have subsequently been reported. Fantl (1996) performed a randomised trial of 83 hypo-oestrogenic patients with urodynamically proven genuine stress incontinence and/or detrusor instability. Women were treated for three months with cyclical conjugated equine oestrogens 0.625mg and medroxyprogesterone 10mg or a placebo. At the end of the study period the clinical and quality of life variables had not changed significantly in either group. While this may have been due to the lack of efficacy of the oestrogen prescribed, the mixed pathology of some of the women and the concurrent use of progestogens makes it difficult to draw any firm conclusions.

Jackson and co-workers (1999) treated 67 postmenopausal women with genuine stress incontinence or mixed incontinence with oestradiol valerate 2mg or placebo daily for 6 months in a double blind, placebo controlled study. Six of the 33 women randomised to receive oestradiol experienced breakthrough bleeding during the trial and were subsequently treated with an additional monthly progestogen. Although this is one of the largest studies yet reported with the longest duration of treatment, there were again no significant changes in the subjective or objective outcome measures. It should be noted that similar to other reports the mean age of the women treated was 63 years.

It is possible that irreversible changes in the lower urinary tract may already have taken place in this age group, with only those women in the perimenopausal years likely to benefit from this form of treatment. At present it is unclear if oestrogen supplementation can be used as prophylaxis against the development of urinary incontinence.

6.7.2. Oestrogen in combination with other therapies for stress incontinence

Alpha-adrenergic receptors in the urethral sphincter are sensitised by oestrogens helping to maintain muscular tone (Screiter et al 1976). Several studies have utilised this effect and shown that oestrogen may be a useful treatment for stress incontinence if given in combination with an alpha-adrenergic agent such as phenylpropanolamine (**Table 6.3.**). This type of therapy may be particularly useful for women with mild stress incontinence or for those not suitable for surgery.

6.7.3 Oestrogens for urge incontinence

There are a number of causes of urinary frequency and urgency in postmenopausal women (**Table 3.5.**) and investigation is often required to make an accurate diagnosis. Oestrogen has been used to treat urgency and urge incontinence for many years regardless of the underlying pathology and even in women who initially developed their symptoms many years before the menopause. Perhaps for these reasons very few trials have shown oestrogen to be of benefit for this condition, although again there is a lack of large, randomised controlled studies with a long duration of treatment from which to make conclusions (**Table 6.4.**). Walter (1978) found that a combination of oestradiol 2mg and oestriol 1mg daily cured the symptoms of frequency, urgency and urge incontinence in 7 out of 11 women, whereas placebo cured only 1 of 10 patients.

STUDY	NUMBER OF WOMEN	TREATMENT	DURATION OF THERAPY	RESULTS
Ek 1980	13	Oral oestradiol alone for 1/12 then with norephedrine/placebo	2 months	Oestradiol alone no subjective benefit. Combination therapy produced significant improvement in symptoms and MUCP but no better than norephedrine alone.
Beisland 1984	20	Vaginal oestriol and oral PPA	8 weeks	Combination therapy produced a better subjective and objective improvement than each alone.
Kinn 1988	36	Oral oestriol and oral PPA	12 weeks	Combination therapy produced a better subjective and objective improvement than each alone.
Ahlstrom 1990	29	Oral oestriol and oral PPA	6 weeks	Combined therapy and oestriol alone both reduced SI, with more women preferring combination. Combined treatment produced a greater objective benefit than each given alone.
Hilton 1990	60	Conjugated oestrogen (oral or vaginal) and/or oral PPA	4 weeks	Vaginal oestrogen better than oral in relieving frequency and nocturia, an effect enhanced by PPA. SI improved in all groups but maximally with vaginal oestrogen and PPA. No objective changes.
Walter 1990	28	Oral oestriol and oral PPA	8 weeks	Subjective improvement with both oestriol and PPA, but better with combination therapy. Objectively, oestriol and PPA together significantly reduced number of leakage episodes, but not pad test loss, compared to oestriol alone.

Table 6.3.: Trials comparing oestrogen in combination with other medical therapies for stress incontinence. With the exception of the study reported by Ek 1980, GSI was confirmed on cystometry. SI = Stress incontinence, UI = Urge incontinence, GSI = Genuine stress incontinence, PPA = Phenylpropanolamine.

Samsioe (1985b) used oral oestriol 3mg daily to treat 34 women aged 75 years in a double blind placebo controlled crossover study (**Table 6.2.**). Although oestriol was found to have no effect on stress incontinence a significant subjective improvement was found in the 12 women with urge incontinence and 8 women with mixed incontinence. Enzelsberger (1991) treated 30 women with urge incontinence using vaginal oestriol (1mg or 3mg) or a placebo. At the end of the three week study period there was a significant improvement in urinary symptoms but only in the women receiving the higher dose of oestrogen. Patients diagnosed as having detrusor instability failed to respond and there were no objective changes. A large placebo effect is known to occur in the treatment of this condition and these reports therefore need to be interpreted with caution, particularly in view of the small number of women treated.

In a double blind multicentre study 64 postmenopausal women with the "urge syndrome" were randomised to treatment with oral oestriol 3mg daily or placebo for 3 months (Cardozo et al 1993b). Urodynamic studies were performed at baseline and compliance was confirmed by a significant improvement in the maturation index of vaginal epithelial cells in the active but not the placebo group. Oestriol produced subjective and objective improvements in urinary symptoms but it was not significantly better than placebo. The authors had hoped to recruit 100 women into the study from 10 centres over an 18 month period. However, four centres did not enrol any patients at all and in another four only a very small number of women agreed to participate. The requirements set out by the power calculation were therefore not met.

Sustained release oestradiol vaginal tablets (Vagifem, Novo Nordsk) or placebo were used by Benness and colleagues (1992) to treat 110 postmenopausal women with lower urinary tract symptoms. At the end of the 3 month treatment period the only significant differences between the active and placebo groups was an improvement in

the symptom of urgency in the women who had a urodynamic diagnosis of sensory urgency. In these women it was possible that the oestrogen was reversing atrophic changes in the lower urinary/genital tract rather than treating any underlying bladder pathology.

These studies may not have shown any benefit possibly because the wrong type of oestrogen was used for too short a time period or it may have been given by the wrong route. Oestriol, although a naturally occurring oestrogen, has little effect on the endometrium and does not prevent osteoporosis. It is therefore also questionable whether the low dose used in these studies is sufficient to treat urinary symptoms. Sustained release oestradiol vaginal tablets are well absorbed and have been shown to induce maturation of the vaginal epithelium within 14 days (Nilsson & Heimer 1992) but higher systemic levels may be needed for therapy to be effective. The other concern regards compliance with treatment, particularly when oestrogen is given vaginally to elderly patients. To try and overcome this and other problems associated with the previous studies 25mg oestradiol implants were administered to women with the "urge syndrome" who were then assessed over a six month period. This study is reported in detail in **Chapter 12.** The safety and rationale for using unopposed oestrogen in this way has already been outlined in **Chapter five.**

STUDY	NUMBER OF WOMEN	SYMPTOMS	URODYNAMICS	TYPE OF OESTROGEN	DURATION OF THERAPY	RESULTS
Walter 1978	29	UI or SI	Yes	Oral oestradiol and oestriol	4 months	No significant change in SI or objective measures. Cure rate in UI significantly better than placebo.
Enzelsberger 1991	40	UI	Yes	Vaginal oestriol	3 weeks	Subjective improvement only in women on 3mg oestriol (not 1mg). No objective changes.
Benness 1992	105	UI	Yes	Vaginal oestradiol	12 weeks	Subjective improvement in symptoms of frequency, nocturia and incontinence but not greater than placebo. Significant improvement in urgency but only in women with sensory urgency. No objective changes.
Cardozo 1993b	64	UI	Yes	Oral oestriol	3 months	Oestriol produced subjective and objective improvements but not significantly better than placebo.

Table 6.4.: Randomised trials comparing oestrogen therapy with placebo for urge incontinence.
SI = Stress incontinence, UI = Urge incontinence.

CHAPTER 7

EATING DISORDERS

7.1 EATING DISORDERS

Studies assessing the impact of oestrogen deficiency on the bladder are usually hampered by the fact that postmenopausal women are almost always older than premenopausal women, and are therefore more likely to have been subjected to the effects of the ageing process. To try and overcome this problem the prevalence of urinary symptoms in young women with severe eating disorders was investigated and the results reported in **Chapter 10.**

7.2. DEFINITION

The two most well established eating disorders, anorexia nervosa (AN) and bulimia nervosa (BN), occur primarily in females during adolescence and young adulthood. The psychopathology of both are complex and varied in form with frequently some overlap between the two groups. The former is characterised by failure to maintain a normal body weight, while the latter is characterised by recurrent episodes of binge eating and extreme weight control measures such as laxative misuse and self-induced vomiting. Disturbances regarding self-perception of body weight and shape are core features of both disorders.

Current diagnostic criteria subdivides AN into a restricting type and a binge eating/purging type, with each group having a different psychological and medical profile. Restricting anorexics tend to be highly controlled, rigid and often obsessive (Wilson et al 1996), whereas those who binge have higher rates of impulsivity and stronger personal and family histories of obesity (Strober 1980). A woman cannot be diagnosed with both AN and BN, so that an emaciated individual who is bingeing and purging will be diagnosed with AN, bulimia subtype. The prognosis may be very different for the two groups. Often BN can be treated successfully with good

probability for complete recovery (Fairburn et al 1995). However, AN remains resistant to successful long-term treatment (Hsu 1991).

7.2.1. Body mass index

The most commonly used method of assessing body composition is the body mass index (BMI). The Belgian astronomer, statistician and epidemiologist Quetelet observed that among adults the average weight appeared to be proportional to the square of the height. He therefore used the formula Kg/m^2 as an index of relative body weight, which is now referred to as the BMI. BMIs between 20 and 25 are very common and generally believed to be healthy, whereas a BMI of approximately 28 or greater is generally taken to indicate obesity (Sichieri et al 1991). BMIs between 10 and 12 appear to represent the lower limit of human survival (Henry 1994). It is not uncommon for hospitalised anorexic patients to achieve BMIs of 15 and lower. In a gynaecological setting, women with a BMI of less than 20 frequently present with amenorrhoea. The hormonal reasons for this are discussed later.

7.2.2. Psychopathology

Women with eating disorders present with a diversity of pathological thoughts and behaviours. A number of self-report measures have been developed to provide a measure of symptom severity and a means of evaluating treatment outcome. These assessments have the advantage over personalised interviews in that they are relatively inexpensive, brief, easily administered as part of epidemiological investigations and are objectively scored.

The Eating Attitudes Test (EAT) is probably the most widely used rating scale in the study of AN. Originally produced with 40 items designed to evaluate a range of

attitudes and behaviours (Garner & Garfinkel 1979), factor analysis yielded a 26 item version (EAT 26) **(Appendix)**, which was highly correlated with total scores on the original EAT (r =0.98) (Garner et al 1982). The EAT 26 is a valid and reliable tool with a high level of internal consistency. It takes less than 10 minutes to complete and each question is scored on a 6 point Likert scale (1 = *never*, 6 = *always*). The items are awarded 3 points for extreme "anorexic" responses, 2 points for the adjacent alternative, 1 point for the next alternative and no points for the remaining three alternatives. Using a "cut off score" of 20 to discriminate between AN and control groups, the EAT 26 questionnaire correctly diagnoses 83.6% of cases. While high EAT scores may indicate the presence of symptoms common to AN, it is inappropriate to assume that a score over 20 in a non-clinical setting is diagnostic for this eating disorder. Although the questionnaire may indicate the presence of disturbed eating patterns, it does not identify the psychopathology behind this behaviour. For example, the EAT 26 has not been found to discriminate between AN and BN (Gross et al 1986, Williamson et al 1993).

The EAT 26 questionnaire is therefore suitable either as an outcome measure in clinical groups or a screening instrument in non-clinical settings.

7.3. EPIDEMIOLOGY

Epidemiological studies of AN are hampered by the fact that eating disorders have a relatively low prevalence in the community and sufferers tend to conceal their illness and avoid professional help (Hsu 1996)(**Table 7.1.**). This makes it necessary to study a very large number of subjects from the general population to reach enough differential power for the cases. Several strategies have been used to circumvent this problem, in particular case register and other record based studies, and assessment of special populations. The limitations of these types of study are considerable. Case register and

REFERENCE	STUDY GROUP	NUMBER OF SUBJECTS	SCREENING TOOL	% PREVALENCE
Szmukler 1985	Private schools	1331	EAT	0.8
Whitaker et al 1990	High school girls	2544	EAT	0.3
Whitehouse & Button 1988	General Practice	540	Questionnaire	0.2
Rathner & Messner 1993	Schoolgirls	517	EAT	0.58

Table 7.1.: The prevalence of anorexia nervosa in young women.

other mainly hospital-based studies include only patients who have come into the mental health care system. Their validity therefore depends upon their diagnostic accuracy and the coverage of cases. Women who have never entered the health care system or have not been diagnosed as having an eating disorder will not be included in the results. Studies of special populations, selected because they are thought to contain an at risk group such as female students, ballet dancers or athletes, may not be applicable to the general population. The current incidence of AN is thought to be at least 8 per 100 000 population per year and the incidence of BN is at least 13 per 100 000 population per year (Hoek et al 1995). An average 1-year prevalence of AN in young females is 0.28% although the studies may have the limitations described above.

7.4. PATHOPHYSIOLOGY

Eating disorders, particularly anorexia nervosa, have been well known since the latter half of the 19th century, when anorexia was first described by Gull (1873) in London and Lasegue (1873) in Paris. It seems likely that patterns of behaviour resembling eating disorders were in existence for centuries prior to their "discovery" but in forms not thought of as illnesses. Many hypotheses about the aetiology of eating disorders have been proposed but it is generally accepted that a precise understanding of their cause remains elusive. However, it is clear that many factors contribute to their development including individual personality, family dynamics, genetic and biological predispositions, and sociocultural factors. The latter are of particular importance in understanding why eating disorders have become more prevalent in the most vulnerable group of young women aged 15-24 years over the last 50 years.

Anorexia nervosa is found in many different countries and is certainly not confined to industrialised parts of the world (Hoek et al 1995). However, it does appear

that anorexia nervosa is more common in countries where food and material prosperity abound. Recent media promotion of tall, thin women and in particular supermodels has been thought to provide a psychological environment in which anorexia nervosa is more likely to develop if there are susceptible underlying personality characteristics. However, there is no consensus that the prevalence of anorexia nervosa has increased as a result of this factor alone (Fombonne 1995). Family relationships may be strained or disordered in anorexia nervosa but it is unclear if this is a cause or effect of the eating disorder (Thienemann & Steiner 1993). Siblings of individuals with anorexia nervosa are much more likely to be affected by an eating disorder than the general population (Strober et al 1985) and this has been taken as evidence of a genetic liability to anorexia nervosa. However, chromosomal analysis using routine karyotyping tends to be normal and it is likely that the increased prevalence in this setting is due to the fact that siblings are usually exposed to a similar psychosocial environment.

In early childhood the ovaries are amorphous with very small follicles. As weight increases at an age dependent rate the ovaries enlarge and demonstrate multiple small follicles. At puberty the ovaries develop a dominant or ovulatory follicle. These changes are accompanied by a rise in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. There is controversy as to whether there is a minimum weight upon which the onset of puberty is dependent. Frisch and Revelle (1971) suggested that there must be at least a critical body composition (17% as stored fat) but others have disputed this view (Billewicz et al 1981). However, it does appear certain that pre-pubertal malnutrition may lead to delay or arrest of pubertal development. As a consequence women suffer hypogonadotrophic hypogonadism with a resulting hypo-oestrogenic state which may be of long duration and continue even after some weight has been gained. Depending upon the timing of onset of AN women

may have either primary or secondary amenorrhoea. Starvation associated with anorexia nervosa leads to changes in the production and functioning of several hormones, particularly along the hypothalamic-pituitary-gonadal axis. In post-pubertal girls there is suppression of the pulsatile secretion of gonadotrophic hormones from the anterior pituitary with levels falling to those of a pre-pubertal, infantile state. As women with anorexia nervosa begin to lose weight even adrenarche, the secretion of androgen hormones such as dehydroepiandrosterone by the adrenal gland about two years prior to puberty, is reversed (Pirke & Platte 1995). Growth hormone levels may also be suppressed and this is particularly important if the speed and timing of the normal growth spurt are affected (Christie et al 1998). Alterations in the level of several other hormones, including corticotrophin releasing hormone (CRH), adrenocorticotrophin hormone (ACTH) and cholecystokinin (CCK) have been reported but are unlikely to have an effect on the female lower urinary tract and are therefore not considered further.

7.5. MEDICAL COMPLICATIONS

Long term follow-up studies of women with AN have shown that even after treatment in a specialised centre only 40% of patients can be regarded as cured (Herzog et al 1992). The remaining patients remain susceptible to the somatic complications of acute and chronic malnutrition. Because patients with AN and BN tend to deny their disease and the resulting physical damage, medical complications of starvation are often the reason they receive treatment for the first time.

The most common physical problems associated with eating disorders are shown in **Table 7.2.**.

ACUTE PHASE	CHRONIC PHASE
Disturbances of electrolyte and acid-base balance	Chronic renal failure
Acute renal failure	Cardiac arrhythmia
Cardiac arrhythmia	Constipation
Impaired gastric emptying	Anaemia
Gastroduodenal ulcers	Amenorrhoea
Opportunistic infection	Infertility
General weakness	Osteoporosis
Hypothermia	Dental defects

Table 7.2.: Common medical complications in eating disorders.

7.5.1. Acute changes

Patients with AN and BN may develop a number of potentially fatal somatic complications which require immediate hospitalisation. Hypokalemia is found in about a third of women with severe eating disorders (Bonne et al 1993), particularly in association with purging behaviour, and at its extreme may result in tachyarrythmias and nephropathy. Deficiencies of sodium, magnesium, phosphate and calcium also occur commonly. Serum glucose levels are low in most cases of AN. Self induced vomiting may give rise to metabolic alkalosis (McClain et al 1993) and laxative abuse metabolic acidosis (Mitchell et al 1987). Disturbances of the immune, haematological, cardiovascular and gastrointestinal systems also occur but are beyond the scope of this review.

7.5.2. Chronic changes

7.5.2.1 Reproductive function

As described earlier, disturbance of the hyothalamo-pituitary-gonadal axis occurs almost universally in women with AN and may result in either primary or secondary amenorrhea, depending on the age of the patient at first manifestation. Failure of follicular maturation and anovulation are associated with infertility (Bates et al 1982).

7.5.2.2. Osteoporosis

Chronic oestrogen deficiency may result in osteoporosis in approximately 17% of women 12 years after first treatment (Herzog et al 1993). Apart from a typical reduced bone density (Treasure et al 1986) pathological fractures have been reported in 44% of cases (Herzog et al 1993). The development of osteopenia can be characterised by two mechanisms which supplement and reinforce each other. Firstly, because of the early onset of the disease there is a reduced peak bone mass (Biller 1989). Secondly, premature and increased bone destruction occurs (Matthews et al 1985). Almost all authors agree that the duration of amenorrhea and oestrogen deficiency are the most important aetiological factors in the development of bone disease in women with eating disorders, and are strongly correlated with the degree of osteopenia.

There is evidence that weight gain can prevent further loss of bone mass and may even lead to an increase in bone density (Bachrach et al 1991). At present there has been only one controlled, prospective study of hormone replacement therapy in a group of 48 women with AN (Klibansky et al 1995). While there does appear to be some therapeutic effect, particularly for women with a body weight of less than 70% of the ideal, the optimal dose of oestrogen and duration of replacement therapy remain

unknown. Furthermore, it is clear that sufficient intake of vitamin D and calcium is essential for therapy to be effective.

7.5.2.3. Urinary symptoms

In the first report of the prevalence of urinary symptoms in women with eating disorders, my colleague Kelvin Boos and myself performed a pilot for the study reported in **Chapter 10** (Boos et al 1999). The urinary symptoms of twenty nine women with severe AN were prospectively evaluated using a structured questionnaire. The median age of the women was 23.8 years (range 17-40 years) and mean BMI 14 (range 13-16). The median age of onset of AN was 17 years (range 13-36 years) with a median duration of 6 years (range 3-19 years). Three women suffered primary and twenty six women secondary amenorrhoea with a median duration of absent menses of 4.4 years (range 1-6 years). The type and frequency of the urinary symptoms described by the subjects is shown in **Table 7.3.**.

URINARY SYMPTOM	NUMBER OF WOMEN (%) (n=29)
Frequency	17 (59)
Nocturia	15 (52)
Urgency	18 (62)
Urge Incontinence	7 (24)
Stress incontinence	2 (7)
Recurrent urinary tract infection	9 (31)

Table 7.3.: Prevalence of urinary symptoms in women with severe anorexia nervosa. Adapted from Boos et al (1999).

Our study therefore found that the prevalence of urinary symptoms in women with severe AN was much higher than that expected in the general population. This finding was very important because it suggested that young women with severe oestrogen deficiency may also develop similar urinary symptoms to those found after the menopause. However, an age matched control group was not used for comparison and no estimation of the level of oestrogen deficiency was made. Therefore, to investigate the prevalence of urinary dysfunction in this group of oestrogen deficient women further, the study described in **Chapter 10** was performed.

CHAPTER 8

OESTROGEN AND URINARY TRACT INFECTION

8.1. URINARY TRACT INFECTION

Urinary tract infections (UTI) may occur in women of all ages but they are particularly prevalent in the elderly. The menopause and subsequent oestrogen deficiency have been implicated as aetiological factors in this process. However, studies assessing the efficacy of oestrogen replacement therapy for prophylaxis against recurrent urinary tract infections in women have given conflicting and largely disappointing results. It is therefore possible that changes in the prevalence of UTI as women become older are a result of the ageing process, rather than as a consequence of pathophysiological changes occurring in the urogenital tract as a result of the menopause.

8.2. DEFINITION

Urinary tract infection describes a condition in which there are micro-organisms present and multiplying within the urinary tract either in the bladder, prostrate, collecting systems or kidney (Cattell 1996). It is usually caused by bacteria but may involve a fungal or more rarely a viral pathogen. A UTI is therefore almost always characterised by the presence of bacteria in the urine, with the exceptions of bacterial prostatitis, infected renal cysts or a perinephric abscess. *Bacteriuria* literally indicates the presence of bacteria in a voided sample of urine.

Urine can be obtained from the bladder for microbiological examination using a number of different methods including suprapubic aspiration, insertion of a urethral catheter or sampling from a catheter bag. However, collection of a mid-stream urine (MSU) specimen is by far the most frequently used technique both in hospital and general practice.

Clear instructions are required by most patients (preferably in a printed form) before they attempt to collect an MSU sample. It is recommended that the hands are

washed and in women that the periurethral area is cleaned in a front to back motion before collection. The distal urethra is colonised with organisms in almost all females and approximately a third of males and therefore the initial part of the urine stream is most likely to be contaminated (Henning & Tornvall 1975, Marrie et al 1978). Using the MSU technique the initial urine flow is discarded by the patient and the following middle part collected by inserting a sterile pot into the stream a moment or two after starting voiding. Unfortunately, there are a number of sources of contamination including the flora of the hands, labia, vagina and perineum. It is also recognised that many urine samples are collected without cleaning or using only a cursory attempt and therefore this technique, while widely practised, has some limitations.

Urinary tract infection occurs when a single strain of bacteria gains entry to the bladder or kidney and begins rapid multiplication either on or in the urothelium or adjacent urine. Kass (1956) suggested that counts of 10^5 organisms/ml or above indicated infection. This threshold has been adopted by most laboratories, including the microbiology department at King's College Hospital, since it allows reports to be made on a clearly determined end point. Counts below 10^3 organisms/ml and sometimes 10^4 organisms/ml are regarded as indicating contamination. Bacterial counts of 10^4-10^5 organisms/ml in a pure growth may mean that the patient has a urinary tract infection but the result needs to be related to the patient's symptoms and circumstances for an accurate diagnosis to be made. In a laboratory context a robust definition is essential, as many samples will culture some organisms. The breakpoint counts of 10^3/ml and 10^5/ml are therefore widely used to distinguish infection from contamination respectively. Changing these thresholds obviously alters the sensitivity and specificity of urine culture for diagnosing urinary tract infection.

The relevance of bacterial counts below 10^5/ml in patients with symptoms remains contentious. Low counts of organisms may be obtained if the patient is already on antibiotics, there is a high fluid intake (perhaps on the advice of a doctor) or when the urinary pH is low. It is good practice to be aware that infection may be present when there are low counts of pathogens but further research on the pathogenic role of low numbers of organisms is necessary. There are a number of other reasons why a patient may have urinary symptoms in this situation and the results of cultures less than 10^5 organisms/ml need to be interpreted with caution. Mixed cultures of organisms should be repeated even in the presence of pyuria and relevant urinary symptoms, with particular care made to avoid contamination (Sanderson 1998).

8.3. EPIDEMIOLOGY

Urinary tract infection is a common condition occurring in the general population with a prevalence strongly related to age and gender. The number of population based reports are very limited mainly because studies of the necessary size and duration are expensive and difficult to conduct. Varying definitions of UTI and bacteriuria, intervals between sampling and the spontaneous resolution of infections also make interpretation of the available results difficult (Monane et al 1995). Many women with symptoms of a urinary tract infection may not present to their doctor, and even in those that do antibiotics may be given without confirmation of an infection on urine culture. The setting for a study may also influence the prevalence of bacteriuria. For example, the prevalence of UTI in ambulatory elderly people living in the community is lower than of people living in old people's homes, which in turn is lower than the prevalence of UTI in patients living in long term residential or hospital based care (Brocklehurst et al 1968, Lye 1978, Boscia et al 1986).

Epidemiological studies documenting the prevalence of bacteriuria in the community were initially performed 20-30 years ago (**Table 8.1.**). Unfortunately, less attention has been focused on urinary tract infection in the recent past (Ronald 1996). The observed levels of infection from the different study populations are remarkably consistent and all show the same trend of increasing prevalence with age. Nuns have a lower prevalence of bacteriuria than the other study populations and this suggests that sexually active women have a higher prevalence of bacteriuria than those who are not. None of the studies in **Table 8.1.** specifically examined the effect of the menopause and oestrogen deficiency on the prevalence of UTI. However, there does not appear to be a dramatic change in the rate of increase of bacteriuria in the age groups above the expected mean age of the menopause in any of the reports. This is considered further below.

In **Table 8.2.** the differences in the prevalence of bacteriuria between men and women, and those living in different environments, are demonstrated. Although the prevalence of infection is much higher than in the studies listed in **Table 8.1.**, this is a reflection of the older population of subjects under investigation in these reports.

STUDY	POPULATION STUDIED	NUMBER OF WOMEN	AGE (YEARS)	PREVALENCE OF BACTERIURIA (%)
Miall et al 1962	Jamaican women	2365	15-24	1.4
			25-34	2.4
			35-44	3.6
			45-54	4.1
			55-64	8.6
Freedman et al 1965	Hiroshima survivors	3191	<20	0.8
			20-39	1.6
			40-49	3.1
			50-59	2.8
			60-69	7.4
			≥ 70	10.8
Kunin & McCormack 1968	US working women	2698	15-34	4.8
			35-54	4.5
			≥ 55	6.4
	US nuns	3304	15-34	0.3
			35-54	1.5
			≥ 55	4.7
Takala 1977	Middle aged Finnish women	1223	40-49	2.5
			50-59	5.1
			60-64	8.5
Evans et al 1978	Working class community population, Boston, US	7834	16-19	1.1
			20-29	1.7
			30-39	3.7
			40-49	2.5
			50-59	4.3
			60-69	5.8

Table 8.1.: Prevalence of bacteriuria with age in women.

TYPE OF PATIENT	% WITH BACTERIURIA	
	Males	Females
Living at home		
Brocklehurst et al 1968	13	20
Akhtar et al 1972	5.9	17
Living in elderly people's home		
Dontas et al 1981	14	28.6
Kasviki-Charvati et al 1982	19	27.2
In hospital or nursing home		
Walkey et al 1967	31	34
Baldassarre & Kaye 1991	20	25

Table 8.2.: Prevalence of bacteriuria in the elderly with reference to the place of residence.

8.4. PATHOPHYSIOLOGY

8.4.1. Host factors

In women, there are a number of important barriers to the entry and proliferation of bacteria in the bladder. In addition to the anatomical integrity of the lower urinary tract, almost continuous flow of urine in to the bladder has a diluting effect with regular and complete voiding providing a very effective hydrokinetic defence mechanism. The low pH of urine, relatively high urea concentration and local secretion of IgA, which interferes with bacterial attachment, also help to prevent colonisation (Choudhury & Brocklehurst 1998). Normal perineal and periurethral flora, including lactobacilli, anaerobic organisms, streptococci and coagulase-negative staphylococci, are thought to prevent other micro-organisms from becoming established in these areas and so prevent colonisation with uropathogens.

There are many different reasons why women may develop a urinary tract infection and frequently patients may have a combination of risk factors. The most common are detailed in **Table 8.3.**. Urinary tract infection almost always follows invasion of the pathogens through the ascending route via the urethra, with the exception of UTI caused by *Salmonella* or *Mycobacterium tuberculosis*. The female urethra is shorter than the male and is therefore closer to the perineum and vagina, which may become colonised with urinary pathogens particularly if the patient has poor perineal hygiene or soiling secondary to urinary or faecal incontinence. Poor fluid intake, infrequent toileting and incomplete bladder emptying all predispose to urinary tract infection as they result in urinary stasis (Eykyn 1998). This may also be caused by anatomical problems such as ureteric reflux, urethral strictures and urogenital prolapse. Impairment of mobility may reduce the patient's access to fluid and difficulty getting to the toilet can result in urinary retention (Brocklehurst et al 1977). The urine itself may

AETIOLOGICAL FACTOR	CAUSE
Periurethral contamination	Faecal and urinary incontinence
	Increased dependency
	Hospital environment
Increased urinary stasis	Poor fluid intake
	Impaired mobility
	Infrequent toileting
	Voiding difficulty (hypotonic detrusor / bladder outflow obstruction)
	Faecal impaction
	Urogenital prolapse
Intravesical foreign body	Tumour
	Calculi
	Indwelling catheter / other instrumentation
Miscellaneous	Diabetes mellitus
	Immunosuppressive therapy
	Sexual intercourse
	Diaphragm for contraception
	Frequent intercourse / multiple sexual partners
	Reflux nephropathy
	Debilitating illness
	Menopause and oestrogen deficiency?

Table 8.3.: Common predisposing host factors for female urinary tract infection.

also become an attractive culture medium to bacteria if the patient has diabetes mellitus and consequent glycosuria. Foreign bodies such as bladder calculi, tumours and indwelling catheters also provide a site where bacteria multiply and persist despite treatment to provide a chronic source of infection and predispose to recurrent symptoms.

Generations of women have recognised the association between sexual intercourse and the development of urinary symptoms. Nulliparity and a rigid perineum contribute to the development of postcoital dysuria, also known as "Honeymoon cystitis." Organisms are massaged into the urethra and bladder during intercourse and if they are not voided out soon after, they multiply and cause infection. Buckley and co-workers (1978) found an increase in the urinary bacterial count in 30% of women after coitus, and Nicolle and associates (1982) reported that both symptomatic and asymptomatic bacteriuria was more common the day after intercourse. Several behavioural factors have been shown to enhance the risk of urinary tract infection following sex. These include deferred voiding after sexual intercourse (Strom et al 1987), frequency of sexual intercourse (Foxman & Frerichs 1985), low fluid intake (Ervine et al 1980) and deferred voiding after the initial urge to micturate (Adatto 1979).

A recent large study has examined the risk factors for urinary tract infection in young women. Hooton and colleagues (1996) prospectively recruited 796 healthy, sexually active women who were included on the basis that they were starting a new contraceptive method and were willing to participate in the study. Two cohorts of women were investigated for a total of 323 person-years of follow-up. The annual incidence of acute cystitis was 0.7 episodes per person-year among university women (90% were confirmed infections on culture) and 0.5 per person-year among women

enrolled in a health maintenance programme. Using multivariate analysis the authors were able to identify contraceptive diaphragm and spermicide use, recent sexual intercourse and a history of recurrent urinary tract infection as independent risk factors for urinary tract infection among women at each study site. The relative risk of urinary tract infection increased from 1.0 for unmarried women who had not been sexually active in the previous week to 9.0 for women who had had intercourse seven times during that period.

As women become older they are more likely to develop one of the risk factors listed in **Table 8.3.** and this may in part explain the changes in prevalence of UTI with ageing. The effect of changes in immune response in the elderly is controversial. At present, there is no conclusive evidence that impairment of immune function as a result of ageing per se is an independent risk factor for the development of urinary tract infection (Horan & Parker 1998). However, once an infection is acquired the old are usually sicker and at considerably greater risk of dying than the young.

The role of the menopause and oestrogen deficiency is considered below.

8.4.2. Microbiology

Escherichia coli is the most frequent urinary pathogen isolated from between 50-90% of all uncomplicated urinary tract infections arising in the community (Gruneberg 1994)(**Table 8.4.**). Colonisation of the gastrointestinal tract by the organism occurs soon after birth when the source of the organisms is usually maternal. Several virulence factors are known to be involved. Adherence of the bacteria to the vaginal interoitus and subsequently the urothelium is important in the initiation of infections in the lower urinary tract. Uropathogenic strains of Escherichia coli have several fimbrial types including both type 1 (mannose sensitive) and type 2 (mannose resistant)

ORGANISM	PERCENTAGE (%)
E. coli	69.4
Enterococci	5.5
Klebsiella	4.7
Proteus	4.3
Others	16.1
Total	100

Table 8.4.: Organisms causing urinary tract infection. Adapted from Gruneberg (1994).

haemagglutinins which are important for cell adhesion (Steadman & Topley 1998). In addition, an extracellular coat of negatively charged polysaccharides limits phagocytosis by host cells. Possession of somatic (O) antigens, which are responsible for the initiation of inflammation, and therefore symptoms, and capsular (K) antigens also determine the pathogenicity of Escherichia coli in the urinary tract.

Enterococci are found in relatively small numbers in the gut (about 10^4/g faeces). They are commonly associated with infections following instrumentation of the lower urinary tract and have been implicated in the development of recurrent urinary tract infections following the menopause.

Klebsiella species are also part of the normal gut flora and may account for approximately 5% of urinary tract infections. They more commonly cause infection in in-patients than the community dwelling subjects and have been associated with diabetes mellitus (Ly et al 1992).

Proteus can cause urinary tract infection in healthy subjects with no predisposing factors and therefore be regarded as a true uropathogen. Although found in the human gastrointestinal tract, isolation rates from faeces are generally less than 30% (MacLaren 1998). Proteus multiplies rapidly and has been found to possess multiple adhesins and fimbriae which aid its ability to cause ascending infection. However, probably its most important virulence factor is the production of urease, which splits urea into carbon dioxide and ammonia which is toxic to renal cells.

8.5. OESTROGEN DEFICIENCY AND URINARY TRACT INFECTION

Alterations in vaginal physiology and flora following the menopause are thought to place women at an increased risk of urinary tract infection, particularly if they are sexually active (Semmens & Wagner 1982, Semmens et al 1985). There is a rise in vaginal pH and fall in the number of lactobacilli, allowing colonisation with organisms from the gastrointestinal tract which act as uropathogens (Stamey & Kaufman 1975). Oestrogen reverses the changes which occur as a result of the menopause, probably by increasing glycogen production in the vagina leading to recolonisation by lactobacilli and a reduction in vaginal pH (Stamey & Timothy 1975). This effect enables oestrogen to be used for treatment or prophylaxis against recurrent urinary tract infection.

8.5.1. Uncontrolled trials of oestrogen for recurrent urinary tract infection

Initial small uncontrolled studies of oestrogen therapy for prophylaxis against recurrent urinary tract infections produced encouraging results (**Table 8.5.**). Parsons and Schmidt (1982) gave 5 women with severe recurrent cystitis intravaginal conjugated oestrogens until the vaginal flora reverted to that seen in premenopausal women. Of the 5 women, 4 had no further urinary tract infections in up to 15 months of follow up.

Brandberg and colleagues (1987) treated 41 female geriatric inpatients with recurrent urogenital infections using oral oestriol (3mg per day for one month and 1mg per day thereafter). The mean age of the women was "between 80 and 90 years" and no indication was given of the mean duration of symptoms. After one month of treatment the vaginal flora of all women showed a dominance of lactobacilli. The prescription of antibacterial agents for urogenital infections given before the trial started was analysed retrospectively and found to be 16 times greater than that during the study period.

Privette and associates (1988) studied 12 postmenopausal women who experienced frequent urinary tract infections and were also found to have atrophic vaginitis. The mean age of the patients was 61 years (range 51-73 years) with a mean duration of time after the menopause of 12.2 years. Oral conjugated oestrogens were given to all women initially but 3 were changed to vaginal therapy because they developed side effects consistent with the systemic actions of oestrogen. Prior to oestrogen therapy, the frequency of infection was four episodes per patient per year. During a follow-up observation period ranging from 2-8 years there were only 4 infections in the entire group. It is difficult to draw any reliable conclusions from this study as the women were also taking prophylactic antibiotics, forced fluids and Betadine douches both before and after the start of oestrogen therapy.

STUDY	STUDY GROUP	TYPE OF OESTROGEN	ROUTE OF DELIVERY	DURATION OF THERAPY	RESULTS
Parsons & Schmidt 1982	5 women with severe recurrent cystitis	Conjugated	Vaginal	Up to 15 months	4 out of 5 women remained free of infection
Brandberg et al 1987	41 female geriatric inpatients with recurrent urogenital infections	Oestriol, 3mg per day for one month then 1mg per day thereafter	Oral	9 months	Vaginal flora returned to the premenopausal type and the women required significantly fewer antibiotics
Privette et al 1988	12 postmenopausal women with recurrent urinary tract infection who were found to have atrophic vaginitis	Conjugated	Oral (3 women changed to vaginal because of side effects)	2-8 years	During the follow up period there were only four infections

Table 8.5.: Uncontrolled studies of oestrogen for recurrent urinary tract infections.

8.5.2. Case controlled trials of oestrogen for recurrent urinary tract infection

Orlander and colleagues (1992) examined the automated database of 276 general practices in the United Kingdom. Women aged 50-69 years coded as presenting with their first UTI were selected, although no information was available about the results of urine culture. Each woman with a UTI was matched to five randomly selected female controls by age (within 3 years) and practice. Only 18% of the study subjects and 10% of the control cases were currently taking HRT, with less than 4% in each group on long term therapy (greater than 12 months). Long term oestrogen use was associated with a two fold increase in the risk of UTI, odds ratio (OR) 2.0 (95% CI 1.7 - 2.5). However, this effect was only seen in women with a uterus and not those who had previously undergone a hysterectomy. The data did not provide an obvious reason to account for these differences.

More recently, Oliveria and co-workers (1997) performed a case controlled study of 254 women aged 45-89 who were identified from a database as having a culture proven UTI. For each case up to five control women were selected, matched by year of birth. The patients were all members of a community health plan, and pharmacy records were searched for evidence of HRT use. This was similar to that reported by Orlander above, with 20% of the women with a UTI taking HRT and 17% of the controls. The authors could find no difference in the risk of developing a UTI between those women currently taking HRT and patients who apparently had never used oestrogen replacement. The results therefore did not suggest a protective effect of HRT on the risk of developing a UTI.

The results of these case controlled studies are summarised in **Table 8.6.**.

STUDY	STUDY GROUP	SETTING	RESULTS
Orlander et al 1992	3616 women (aged 50-69) coded as presenting with their first UTI 19162 aged matched controls	Database of 276 GP practices	Women using oestrogen for > 1year had an increased risk of being diagnosed with a UTI compared to non-users, OR 2.0 (95% CI 1.7-2.5) This excess risk was only diagnosed in women with a uterus
Oliveria et al 1997	254 women (aged 45-89) with a culture proven UTI 1268 age matched controls	Members of a community health plan	The risk ratio for UTI was 1.08 (95% CI 0.76-1.54) for current users of HRT versus women who had never used HRT The data did not support a protective effect of HRT on the risk of developing a UTI

Table 8.6.: Case controlled studies of oestrogen for prophylaxis against recurrent urinary tract infection.

8.5.3. Randomised controlled trials of oestrogen for recurrent urinary tract infection

Randomised trials of oestrogen for the prevention of recurrent urinary tract infection have produced rather mixed results (**Table 8.8.**). Kjaergaard and colleagues (1990) randomised 21 postmenopausal women with recurrent cystitis to vaginal oestradiol tablets or a placebo. At the end of the five month study period the number of positive urine cultures was not statistically different between the two groups.

Kirkengen and associates (1992) randomised 40 elderly women with recurrent urinary tract infections to receive either oral oestriol 3mg / day for 4 weeks followed by 1mg / day for 8 weeks or matched placebo. The study was double blind and all chemotherapeutic agents were stopped at least two weeks before inclusion. However, the study population was rather heterogeneous in that 19 women were hospital inpatients and 21 women were living in the community. After the first treatment period both therapies reduced the incidence of urinary tract infection but no difference was found between oestriol and placebo. However, following the second treatment period oestriol was significantly more effective than placebo in reducing the incidence of urinary tract infection. In the oestriol group vaginal pH decreased from 6.5 in week one to 5.5 in week 12 with no significant changes occurring in the group receiving placebo.

In a large double blind, placebo controlled study Raz and Stamm (1993) recruited 93 postmenopausal women with recurrent urinary tract infection and randomised them to either treatment with *intravaginal* oestriol cream or a placebo. Midstream urine cultures were obtained at enrolment, monthly for eight months and whenever urinary symptoms occurred. Changes in the vaginal pH and colonisation with lactobacilli were present within in the oestriol group only within 1 month of the start of treatment. The incidence of urinary tract infection in the group given oestriol was

significantly reduced as compared with that in the group given placebo (0.5 versus 5.9 episodes per patient per year). However, the incidence of urinary tract infection was extremely high in this study group and it is therefore unclear if the results are applicable to other populations of women with less frequent problems.

Unfortunately a double blind placebo controlled study of *oral* oestriol 3mg daily for the prevention of recurrent urinary tract infections in 72 elderly women did not reproduce these results (Cardozo et al 1998). All women recruited were over the age of 60 years and had had at least two documented urinary tract infections in the previous 18 months. The study was apparently difficult to conduct because of its design and the age of the participants with a dropout rate of 31%. Although both oestriol and placebo improved urinary symptoms during the trial, the incidence of urinary tract infection did not differ significantly between the two groups. At the end of the treatment period the percentage of women remaining infection free was 43% for the oestriol group and 49% for the women receiving placebo. It is possible that the results of this study did not match those of Raz and Stamm (1993) because of the oestriol was given orally, rather than vaginally, and therefore may not have provided an identical therapeutic dose of oestrogen.

In the largest study to date, Eriksen (1999) recruited a total of 108 women into a multicentre, randomised, open, parallel-group study with an untreated control group. Postmenopausal women with recurrent, symptomatic, bacteriologically confirmed UTI were randomly assigned to have either an Estring (2mg oestradiol) for 12 weeks or no oestrogen treatment. Follow up was continued for 36 weeks for the Estring group and either 36 weeks or until the first recurrence for the control group. The proportion of women remaining infection free was significantly higher in the Estring group than in the control group (P=0.008). In addition, after 36 weeks of study the cumulative likelihood

of remaining free of disease was 45% in the women with a vaginal ring compared with approximately 20% in the control group. However, it is difficult to be certain that the results were secondary to the effect of oestrogen rather than having a foreign body (the Estring) in the vagina. It would perhaps have been better if some of the women in the control group had been given a vaginal ring which did not release oestrogen.

The HUT committee have recently reported a systematic review of estrogens for recurrent UTI's and concluded that vaginal oestrogen administration seemed to be effective for this condition (Cardozo et al 1999). However, it is important to note that although UTI is one of the most common reasons why a woman may present to her doctor, fewer than 400 women have taken part in randomised studies of oestrogen for this condition.

The relatively few studies of oestrogen for prophylaxis against recurrent urinary tract infections have therefore produced rather variable results. It is clear that oestrogen induces changes in the vaginal epithelium and flora which appear to be favourable for the prevention of colonisation with urinary pathogens. However, as this effect does not consistently produce an improvement in infection rates above that of placebo, it is possible that the menopause and subsequent oestrogen deficiency are not the primary aetiological factors in the development of recurrent urinary tract infections in elderly women. It can be hypothesised that the effects of ageing on the urogenital tract are more important than those of oestrogen deficiency, which may have been overstated. If this was the case then the incidence of urinary tract infection should increase steadily with age (assuming ageing occurs at a constant rate), with no obvious changes occurring at or after the time of the menopause. This is examined further in **Chapter 11.**

STUDY	STUDY GROUP	TYPE OF OESTROGEN	ROUTE OF DELIVERY	DURATION OF THERAPY	RESULTS
Kjaergaard et al 1990	21 postmenopausal women with recurrent cystitis *10 active group* *11 placebo*	Oestradiol	Vaginal tablets	5 months	Number of positive cultures not statistically different between the two groups.
Kirkengen at al 1992	40 postmenopausal women with recurrent UTI's *20 active group* *20 placebo*	Oestriol	Oral	12 weeks	Both oestriol and placebo significantly reduced the incidence of UTI's ($P<0.05$). After 12 weeks oestriol was significantly more effective than placebo ($P<0.05$).
Raz & Stamm 1993	93 postmenopausal women with recurrent UTI's *50 active group* *43 placebo*	Oestriol	Vaginal cream	8 months	Significant reduction in the incidence of UTI's in the group given oestriol compared to placebo ($P<0.001$).
Cardozo et al 1998	72 postmenopausal women with recurrent UTI's *36 active group* *36 placebo*	Oestriol	Oral	6 month treatment period with a further 6 months follow-up	Reduction in urinary symptoms and incidence of UTI's in both groups. Oestriol no better than placebo.
Eriksen 1999	108 women with recurrent UTI's *53 active group* *55 no treatment*	Oestradiol	Estring	36 weeks for the active group 36 weeks or until first recurrence for the controls	Cumulative likelihood of remaining free of infection was 45% in active group and 20% in control group ($P=0.008$).

Table 8.7.: Randomised studies of oestrogen for prophylaxis against recurrent urinary tract infection.

SECTION TWO

CHAPTER 9

HORMONAL INFLUENCES ON URINARY SYMPTOMS AND THE RESULTS OF URODYNAMIC INVESTIGATION

9.1. RATIONALE

The background to this study has been discussed in **Chapter six**. There is anecdotal evidence to suggest that many women recognise a change in their urinary symptoms during the menstrual cycle. However, the extent of this problem has not been evaluated. In addition, data from retrospective reports suggests that the timing of cystometry with respect to the menstrual cycle may influence the results of urodynamic investigation. A cross sectional study was therefore performed to establish if the menstrual cycle had a clinically significant effect on female lower urinary tract symptoms and the results of urodynamic investigation.

9.2. NULL HYPOTHESIS

This study was designed to test the hypothesis that the menstrual cycle had no impact on the severity of urinary symptoms and the diagnosis of abnormal detrusor activity on videocystourethrography.

9.3. OBJECTIVES

9.3.1. Primary objective

The primary objective of this study was to assess the menopausal status of women referred to the urodynamic clinic at King's College Hospital. I then wished to determine the proportion of premenopausal women who complained of a cyclical change in their urinary symptoms and establish if the most bothersome period coincided with the luteal (progestogenic) phase of the menstrual cycle.

9.3.2. Secondary objective

The secondary objective was to determine if the timing of videocystourethrography with respect to the menstrual cycle had an impact on the diagnosis of abnormal detrusor activity in premenopausal women with a regular menstrual cycle.

9.4. PATIENTS AND METHODS

9.4.1. Study population

Consecutive women referred with urinary symptoms to the urogynaecology department by general practitioners or consultants from other hospitals were prospectively recruited to the study over a six-month period. The following inclusion and exclusion criteria were met.

9.4.2. Inclusion criteria

All consenting English speaking women referred to the urogynaecology unit for videocystourethrography were eligible for inclusion in the study.

9.4.3. Exclusion criteria

Women were excluded from the study if they met one of the following exclusion criteria:

1. Questionnaire not completed satisfactorily.
2. Pregnant.
3. Current urinary tract infection.
4. Urogenital prolapse only with no urinary symptoms.
5. Currently taking anticholinergic medication or hormonal therapy.
6. Routine follow up urodynamics following continence surgery.

9.4.4. Methods

All women recruited to the study completed a questionnaire about their menstrual status and urinary symptoms. Three pilot versions of the questionnaire were produced and tested on women referred for videocystourethrography. Redundant or confusing questions were either modified or excluded before the final version was used **(Appendix)**. On registering their arrival at the reception desk in the urodynamic clinic women were given the questionnaire which they were asked to fill in while waiting for their investigation to be performed. The questionnaire took approximately five minutes to complete and was then handed back to the receptionist, so that it was not seen by the medical team before consultation.

Women were categorised into the following menstrual groups on the basis of answers given in the questionnaire. It was decided not to perform serum analysis for oestradiol or gonadotrophin levels to determine menopausal status further for cost reasons.

1. Premenopausal.
2. Postmenopausal.
3. Less than 12 months of amenorrhoea. Patients in this category were probably postmenopausal but could not be definitely classified as such because they had had at least one period in the last year.
4. Perimenopausal (age 45-55 years) and taking hormone replacement therapy.
5. Previous hysterectomy so menopausal status uncertain.

Women over the age of 55 who were taking hormone replacement therapy or who had previously undergone a hysterectomy were coded as being postmenopausal.

Videocystourethrography was then performed on the same day by myself or one of my urogyanecological registrar colleagues using the protocol described in **Chapter four.** Abnormal detrusor activity was diagnosed when there was low compliance on filling, systolic or provoked detrusor instability. Cystometry was deferred for women complaining of symptoms of urinary tract infection with either leukocytes, protein or haematuria on urinalysis until they had been treated with the appropriate antibiotics. They were therefore excluded from the study.

9.4.5. Statistical analysis

The number of days from the start of the last menstrual period to the date of investigation was categorised as 1-7, 8-14, 15-21, 21-28 days. The data were entered onto a Microsoft Excel spreadsheet, checked for accuracy and then analysed using the statistical package SPSS (version 8.0 for windows). All data entry, processing and analysis was performed by myself. Data relating to diagnosis of abnormal detrusor activity were analysed using the Chi-squared test. This statistical test tabulates a variable into categories and computes an observed and expected frequency for each group. The difference between the observed and expected proportion of values in each category was considered significant when P was less than 0.05.

9.5. RESULTS

548 consecutive women referred for videocystourethrography were asked to complete the questionnaire on arrival in the department. 65 patients were excluded for the reasons outlined in **Table 9.1.**.

REASON	NUMBER OF WOMEN (%)
Follow-up after continence surgery	21 (32%)
Urogenital prolapse only	19 (29%)
Urinary tract infection	6 (9%)
Questionnaire not completed properly	5 (8%)
Did not wish to complete questionnaire	2 (3%)
Currently taking anticholinergic medication	2 (3%)
Gender re-assignment	1 (2%)
Urodynamics considered inappropriate	9 (14%)

Table 9.1.: Reasons why women were excluded from the study. Number of women (Percentage of total number of women excluded).

9.5.1. Demographic details

483 women were included in the study with a mean age of 50.4 years (SD 13.7) and median parity of 2 children (range 0-12). The age distribution is shown in **Figure 9.1.**. 381 (78.9%) women were white, 33 (6.8%) black Afro-Caribbean, 27 (5.6%) Asian, 22 (4.6%) black-African with the remaining 20 (4.1%) women from other races.

154 (31.9%) women had previously undergone a hysterectomy of which 122 (79.2%) had been performed abdominally. 190 (39.3%) patients were currently taking medication other than hormone replacement therapy.

9.5.2. Previous treatment

219 (45.3%) women had previously had treatment for their bladder complaint with some women having received multiple different therapies. This is shown in **Table 9.2.**.

TREATMENT GIVEN	NUMBER OF WOMEN (%)
Pelvic floor exercises	138 (28.6%)
Medication	121 (25.1%)
An operation	76 (15.7%)
Electrical stimulation	31 (6.4%)
Bladder retraining	29 (6.0%)
Other	24 (5.0%)
No treatment	264 (54.7%)

Table 9.2.: Previous treatment given to the women in the study population.

Number of women (percentage of women included in the study).

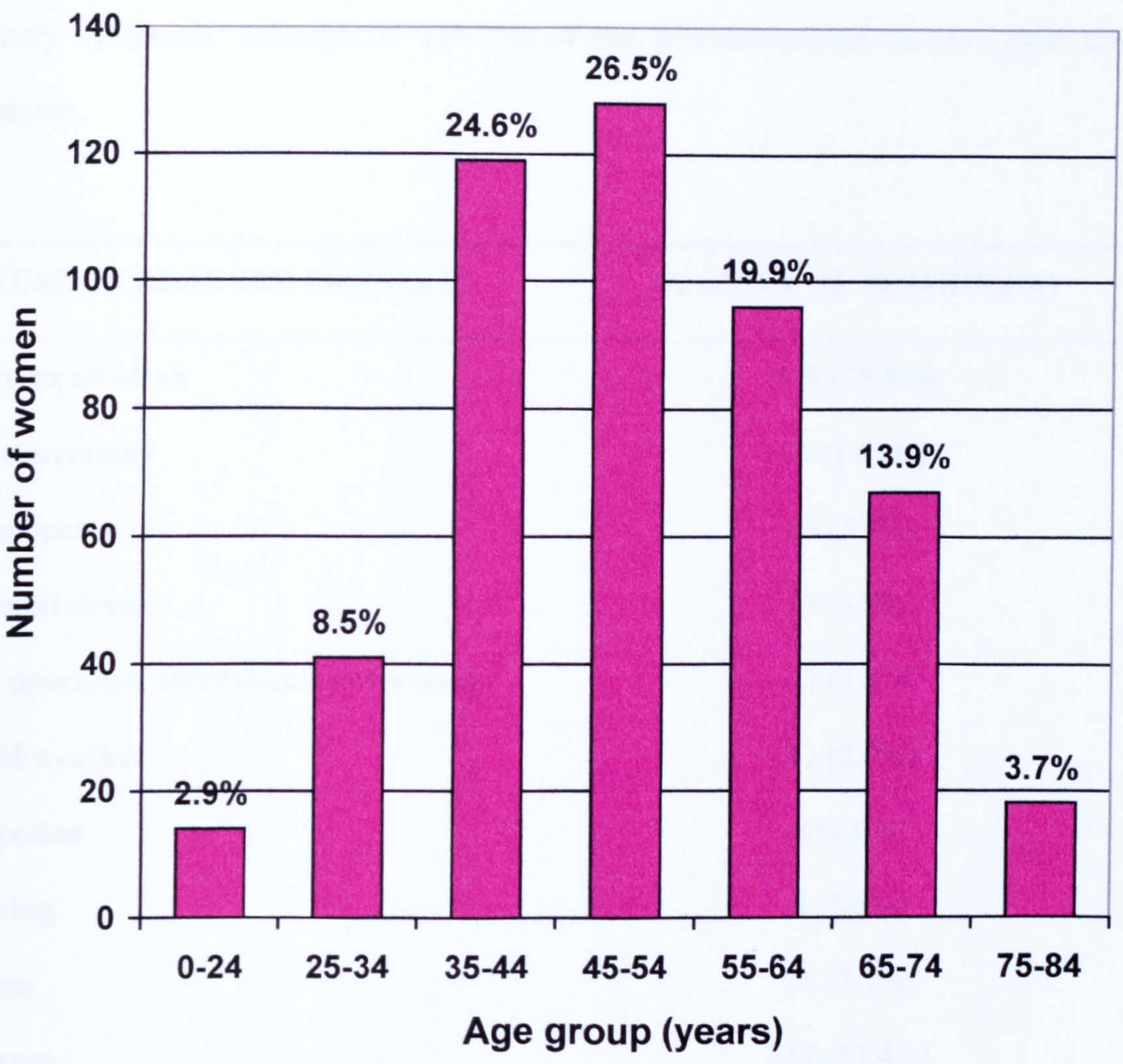


Figure 9.1.: The age distribution of the 483 women referred for videocystourethrography who were included in the study.

9.5.3. Aetiology of urinary symptoms

The patients were asked what they thought was the main cause of their bladder problems to try and determine how many women felt that the menopause was responsible for their urinary complaints. The responses are shown in **Table 9.3.**. Overall only 25 (5.2%) women felt that the menopause was the main cause of their urinary symptoms, although 21 (10.7%) of the postmenopausal women gave this response.

CAUSE OF BLADDER PROBLEM	NUMBER OF WOMEN (%)
Having children	173 (35.8%)
Hysterectomy	70 (14.5%)
Menopause	25 (5.2%)
Mental stress	23 (4.8%)
An operation other than hysterectomy	21 (4.4%)
Cold weather	11 (2.3%)
Infection	8 (1.6%)
Ageing	4 (0.8%)
Other	35 (7.2%)
Unsure	113 (23.4%)

Table 9.3.: The main reasons the women in the study considered to be the cause of their bladder problems.

9.5.4. Menopausal status of the study population

On the basis of answers given in the questionnaire the women were categorised into the groups shown in **Figure 9.2.**. There was an almost identical number premenopausal women (n=194) and postmenopausal women (n=196) in the study group. There were only 6 (1.2%) women who were probably postmenopausal but could not be categorised as such because they had not gone a full 12 months without a period.

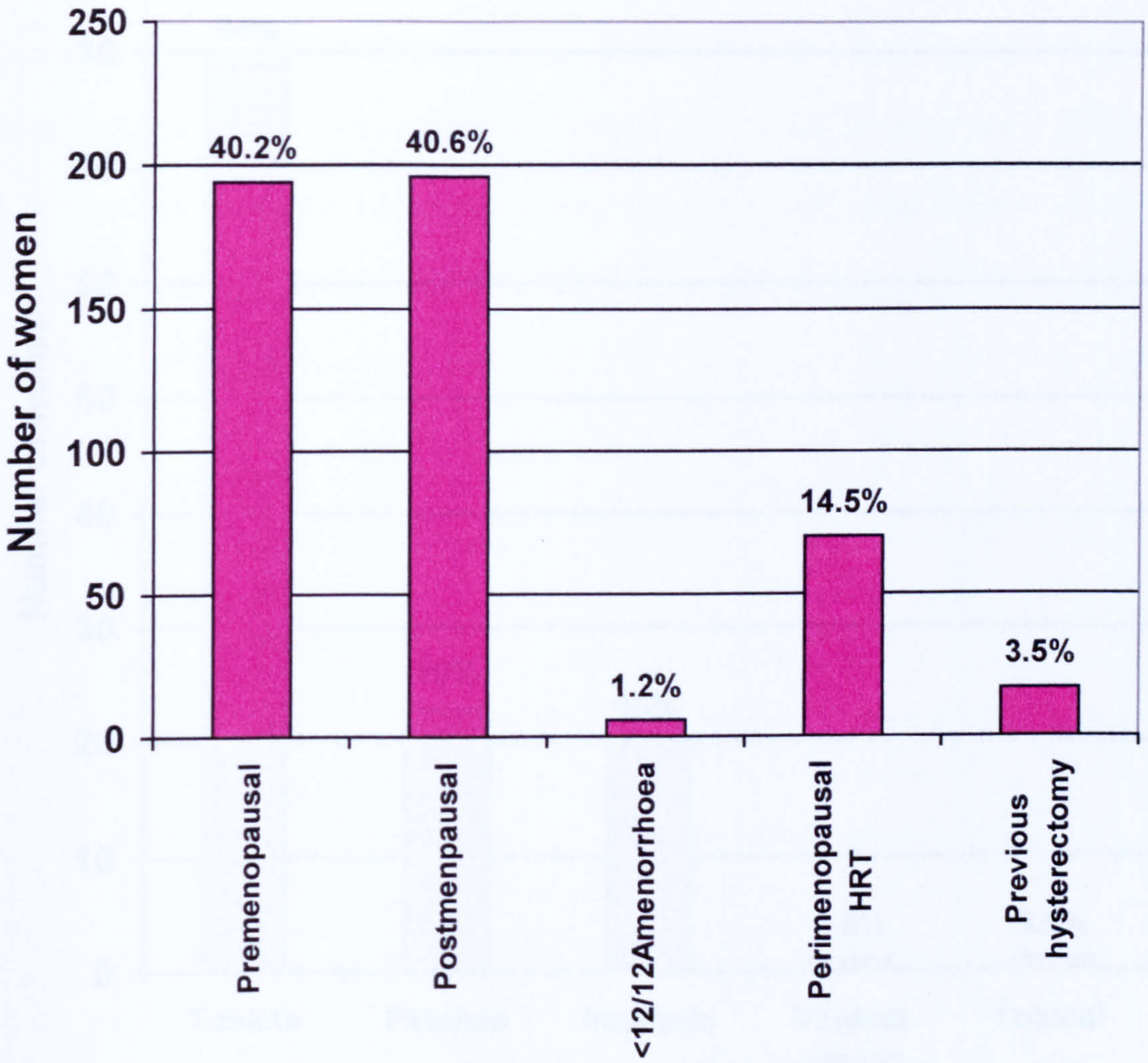


Figure 9.2.: The menopausal status of the 483 women referred for videocystourethrography who were included in the study.

9.5.5. The use of oestrogen and HRT

281 (58.2%) women had taken the oral contraceptive pill in the past but only 20 (4.1%) were currently using this medication. 190 (39.3%) patients had used HRT at some time with 124 (25.7%) women still using this treatment at the time of entry into the study. The methods of HRT administration being used by the women is shown in **Figure 9.3.**.

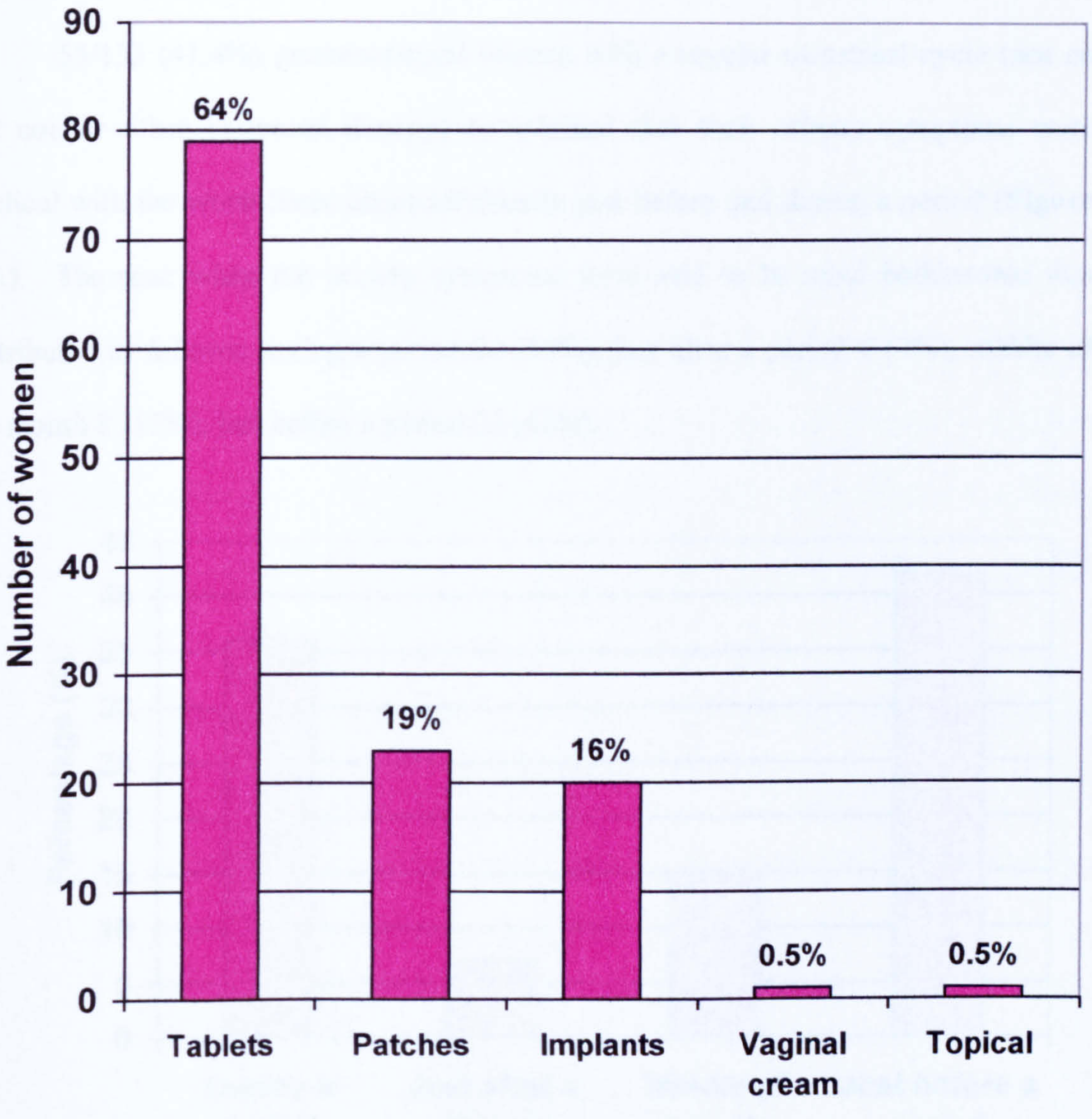


Figure 9.3.: Route of administration of Hormone Replacement Therapy being used by the women in the study.

9.5.6. The menstrual cycle and urinary symptoms

194 (40.2%) women were premenopausal with a mean age of 38.4 years (SD 7.97). 45 (23.2%) women had an irregular menstrual cycle. 149 (76.8%) premenopausal women had a regular menstrual cycle and formed the study group. However, 16 (10.7%) women with regular menses were taking the combined oral contraceptive pill (coc) and therefore excluded from further analysis [4 women with an irregular cycle were also taking the coc].

55/133 (41.4%) premenopausal women with a regular menstrual cycle (not on the coc or other hormonal therapy) complained that their urinary symptoms were cyclical with the worst times characteristically just before and during a period (**Figure 9.4.**). The time when the urinary symptoms were said to be most bothersome was distributed as follows: during a period 20 (36%), just after a period 4 (7%), middle of the month 8 (15%), just before a period 23 (42%).

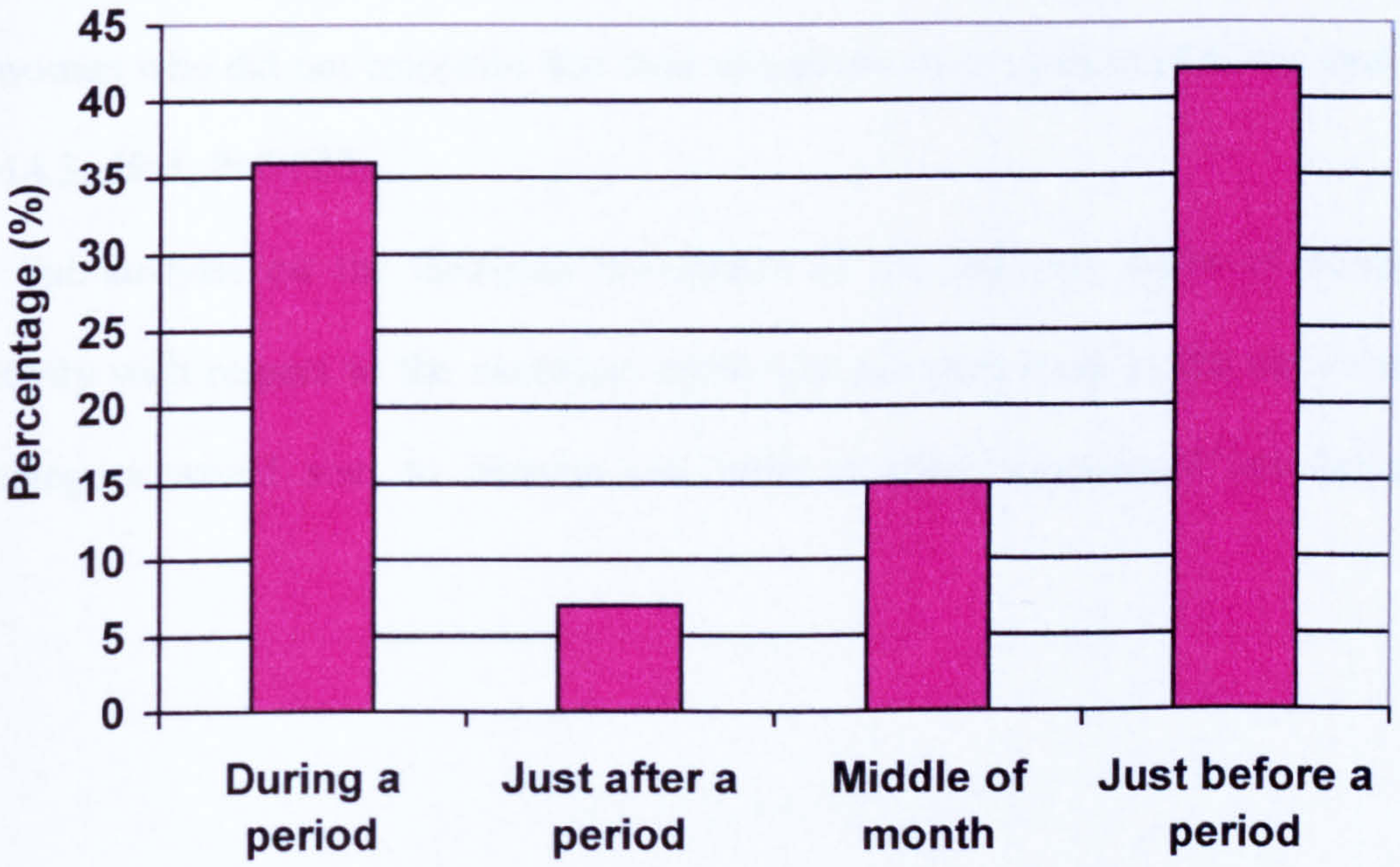


Figure 9.4: Time when urinary symptoms were most bothersome in relation to the menstrual cycle.

9.5.7. Videocystourethrography and the menstrual cycle

The prevalence of abnormal detrusor activity diagnosed on videocystourethrography increased significantly with time from the last menstrual period and may reflect increases in the circulating level of progesterone following ovulation (Chi squared for trend=6.56, df=1, P=0.01) (**Figure 9.5.**). The number of women with abnormal detrusor activity in each group was distributed as follows: day one-seven 7/31 (23%), day eight-fourteen 10/35 (29%), day fifteen-twenty one 12/35 (34%), day twenty two-twenty eight 16/28 (57%). Data were not available for 4/133 (3%) women because of technical difficulties with the urodynamic equipment.

Abnormal detrusor activity was not diagnosed more frequently in those women who complained of cyclical symptoms compared to the patients whose bladder complaint did not fluctuate with the menstrual cycle (Chi squared 1.71, df=1, P=0.19). In addition, the relationship between increasing prevalence of abnormal detrusor activity and number of days from the last menstrual period was still present even in those women who did not complain that their symptoms were cyclical (Chi squared for trend=14.3, df=3, P=0.003).

Sub-analysis on the changing prevalence of the different types of detrusor overactivity with respect to the menstrual cycle was not performed as the numbers in each category would start to become too small to draw meaningful conclusions.

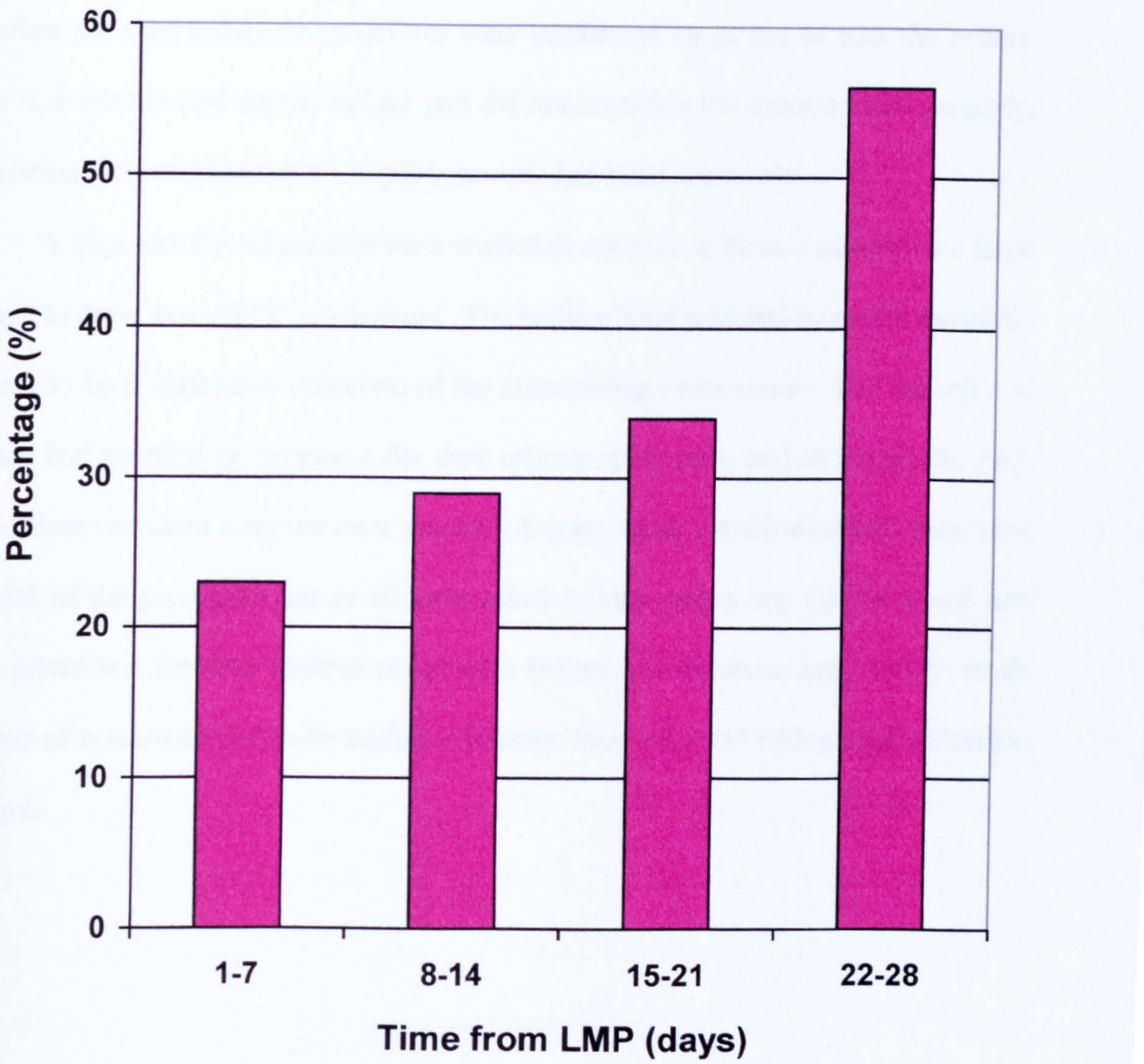


Figure 9.5.: Percentage of women with abnormal detrusor activity on videocystourethrography with respect to time from the last menstrual period.

9.6. DISCUSSION

9.6.1. Study design and population investigated

The primary objective of this study was to assess the menopausal status of women referred for urodynamic investigation. All patients attending the clinic were approached and asked to take part in the study. Questionnaires were completed while the women were waiting to be seen by medical staff and then handed back to the x-ray receptionist. Details of the patients' hormonal status and the nature of their urinary symptoms were therefore not seen before investigations were performed so as not to bias the results. Only five women who agreed to take part did not complete the questionnaire properly, suggesting that modification of the pilot versions had been successful.

A large number of patients were studied in order to achieve a sample size large enough to draw meaningful conclusions. The multicultural population seen in the clinic appears to be a reasonable reflection of the surrounding community. The majority of women had received no treatment for their urinary symptoms, and in those who had, pelvic floor exercises were the most common therapy tried. Medication had been used by 25% of the population but as all were asked to stop taking any tablets which had been prescribed for their bladder seven days before investigation, only a very small number of women needed to be excluded because they were still taking anticholinergic therapy.

9.6.2. Hormonal characteristics of the population studied

The mean age of the 483 women investigated was 50.4 years with approximately an equal proportion of women in the pre-menopausal and post-menopausal groups. These findings are similar to those of community based epidemiological surveys which also report the peak prevalence of incontinence to be almost identical to the average age of the menopause (Thomas et al 1980, Jolleys 1988). Also in common with these studies, the prevalence of incontinence appeared to rise many years before the menopause and fall in the period when oestrogen deficiency is most likely.

Almost 60% of women had used the contraceptive pill at some point but only 20 (4.1%) were currently using this medication. In view of the small number of women in this group it was not really possible to comment on the influence of this therapy on urinary symptoms or the results of videocystourethrography. Using the contraceptive pill to treat women with cyclical urinary complaints is considered below.

Although the largest number of women referred were in the perimenopausal age group, overall only 5.2% of patients felt that the menopause was the main cause of their urinary symptoms. Most women either thought that having children was the most likely cause of their problem or they were unsure why they had developed bladder symptoms. The use of hormone replacement therapy (HRT) in the study population was higher than the 15% previously reported in the UK (Barlow et al 1991, Wilkes & Meade 1991). There are several possible reasons why this may be the case. Firstly, these women had sought help from their family doctors and may therefore be more inclined to consider the health benefits of HRT than the general population who may not have a specific medical complaint. Secondly, some general practitioners may be aware of the possible use of HRT for urogenital disorders and start their patients on oestrogen before referral

to hospital. Thirdly, this finding may be a reflection of the increasing use of HRT over the last decade.

9.6.3. Effect of the menstrual cycle on the prevalence of urinary symptoms and the results of urodynamic investigations

Although it has long been recognised that some women report an increase in irritative bladder symptoms and their ability to maintain continence just prior to menstruation, prospective reports in this area are extremely limited. This study was therefore designed to clarify the impact of the menstrual cycle on the lower urinary tract. Analysis was restricted to patients with a regular menstrual cycle who were not taking hormonal therapy. It can therefore be assumed that at least 95% of these women will have had a hormonal pattern with a pre-ovulatory phase of oestrogen dominance and post-ovulatory phase of progesterone dominance (Balen & Jacobs 1997). This is outlined in detail in **Chapter five.**

Approximately 40% of pre-menopausal women with a regular menstrual cycle (who were not taking hormonal therapy or anticholinergic medication) complained that their urinary symptoms occurred cyclically with the time just before a period characteristically found to be the most bothersome. The possible reasons for this are discussed below. It is uncertain why some women in this study found their bladder complaints particularly troublesome during a period. Although detrusor instability has been previously been described only during menstruation (Lewis & Warrell 1989) overall the prevalence of detrusor activity was at its lowest in the first few days of the menstrual cycle. This finding would therefore not support the hypothesis that cyclical prostaglandin release from the genital tract around the time of a period has a major influence on the bladder. A more likely explanation for the increase in problems at this

time is that women find it much more inconvenient to have urinary symptoms at the same time as they are menstruating.

Attempts were made to try and determine which individual urinary symptoms changed during the menstrual cycle on early versions of the questionnaire. Unfortunately, almost all the women had more than one symptom and despite several modifications it proved impossible to reliably discriminate between the fluctuations of several different urinary complaints. To investigate this area in more detail, and validate the reported cyclical changes, further prospective studies could be performed to assess changes in the severity of different urinary symptoms over time using bladder diaries. Such a study would need to be done over a period of at least three months, but it would probably be the best way of assessing if any objective changes in patient symptomatology could be demonstrated. Measurement of progesterone levels on the 21st day of the menstrual cycle could also be made although this would be time consuming (for both patient and doctor), expensive and unlikely to add significantly to the data in view of the hormonal changes which are already known to occur in women with regular cycles.

The secondary objective of this study was to determine if the timing of videocystourethrography with respect to the menstrual cycle had an impact on the diagnosis of abnormal detrusor activity. When the study was being planned it was decided to only analyse this variable, rather than looking at all urodynamic parameters, because it was felt to be the most likely cause of the reported pre-menstrual increase in irritative bladder symptoms. Again the menstrual cycle appeared to have a significant influence on the prevalence of bladder dysfunction with an increase in the detection of abnormal detrusor activity occurring during the luteal phase. These data are important because they may have implications for the investigation and treatment of

premenopausal women whose initial urodynamics are normal. For example, urodynamic studies may need to be repeated during a different part of the menstrual cycle in such women, otherwise the diagnosis of detrusor instability may be missed and sub-optimal treatment given.

The findings of this study are in contrast with two smaller previous reports which are discussed in **Chapter six.** Sorenson and colleagues (1988) were unable to detect any urodynamic changes attributable to the menstrual cycle in 10 women, although perhaps this was because they were all asymptomatic volunteers in whom there were no cases of detrusor instability. Shimonovitz and associates (1997) identified 57 women with regular periods on their urodynamic database. In this report more abnormal urodynamic diagnoses, including detrusor instability, were made during the follicular phase but only relatively few women were investigated during each stage of the menstrual cycle. In addition, also at variance with our findings was the observation that significantly more normal results were found in the women who felt their symptoms were influenced by the menstrual cycle compared to those who did not. In fact, in our study the relationship between increasing prevalence of abnormal detrusor activity and the number of days from the last period was still present even in those women who did not complain that their symptoms were cyclical.

The changes in urinary symptoms and detrusor activity in our study provide further evidence that the female lower urinary tract is sensitive to the effects of sex steroids. There are several possible mechanisms to account for this. Oestrogen and progesterone are known to influence mood and cognitive function and it may be that a significant part of their effect on the lower urinary tract during the menstrual cycle is mediated via a central action on receptors in the brain and neurological pathways. Although progesterone does not appear to significantly change the urethral pressure

profile (Raz et al 1973, Rud 1980, Van Geelen et al 1981) increases in its level during pregnancy are thought to cause a rise in detrusor instability antenatally compared to that found postpartum (Cutner 1993, Chaliha et al 1998). It is unclear if this is secondary to a central action or a direct effect on the detrusor muscle itself. Therefore, during the menstrual cycle it is possible that the changes which appear to be induced by progesterone may be due to a combination of central and local effects although the exact mechanism of action remains to be determined.

This study suggests that the timing of urodynamic investigation within the menstrual cycle may be important. However, it is uncertain if symptomatic women who have a normal study during the follicular phase of the menstrual cycle should have their study repeated during the luteal phase. It is also interesting to speculate that suppression of the normal menstrual cycle may improve the urinary symptoms of some women and possibly alter the detection of abnormal detrusor activity. However, as hormonal therapies have previously been shown to have a poor efficacy in the treatment of other urinary complaints the outcome of this type of therapy is far from clear. To answer these questions further appropriately designed studies will need to be performed.

It is known that women with incontinence who are taking cyclical HRT may experience a deterioration in their symptoms during the progestogenic phase of treatment (Benness et al 1991). The effect of timing of urodynamic investigation in women on such preparations was not assessed in this study but could be the subject of further research. The effect of continuous combined therapy and the selective oestrogen receptor modulators (SERM) on the female lower urinary tract are also uncertain and considered further in **Chapter 13.**

CHAPTER 10

EATING DISORDERS AND URINARY SYMPTOMS

10.1. RATIONALE

The background to this study has been discussed in **Chapter seven.** Urinary symptoms occur commonly in women of all ages but epidemiological studies in postmenopausal women are complicated by the concurrent effects of the ageing process. Our aim therefore was to determine the effect of oestrogen deficiency on the prevalence of urinary symptoms in younger women.

10.2. NULL HYPOTHESIS

The following study was designed to test the null hypothesis that severe eating disorders and associated oestrogen deficiency had no impact on the prevalence of urinary symptoms in young women.

10.3. OBJECTIVES

10.3.1. Primary objective

The primary objective was to measure the prevalence of urinary symptoms in women with severe eating disorders and a group of age matched controls.

10.3.2. Secondary objectives

The secondary objective was to determine if measures of oestrogen deficiency, including serum oestradiol level and presence of amenorrhoea, were directly related to the presence of the most predominant urinary symptoms in the women studied.

10.4. POWER CALCULATION

Based on our earlier work showing an approximately 60% prevalence of irritative urinary symptoms in women with eating disorders (Boos et al 1999) and assuming a 20% prevalence of irritative urinary symptoms in the general population (Bungay et al 1980), 22 subjects were required in each group to show a difference with 80% power at the 5% significance level.

10.5. PATIENTS AND METHODS

10.5.1. Study population

Women with severe eating disorders (anorexia nervosa or bulimia nervosa) were prospectively recruited to the study from a specialist resident In-patient unit at the Royal Bethlam Hospital. This is a tertiary referral centre run under the supervision of Dr Janet Treasure, Consultant Psychiatrist. During the study period I was assisted in identifying and enrolling eligible patients by Dr Sara Majid, Specialist Registrar in Psychiatry. Radiographers working in the x-ray department at King's College Hospital agreed to act as controls. This group was chosen because the women were likely to be of comparable age to those with eating disorders and also have similar socio-economic backgrounds.

10.5.2 Inclusion criteria

All English speaking women with an eating disorder who were In-patients at the Royal Bethlam Hospital, or radiographers working at King's College Hospital were eligible for inclusion in the study.

10.5.3 Exclusion criteria

Women were not included in the study if they had one or more of the following exclusion criteria:

1. Unwilling to give blood.
2. Pregnant.
3. Controls to have no history of an eating disorder.
4. Did not wish to take part.

10.5.4 Methods

Women eligible to take part in the study were prospectively recruited. Permission to approach the radiographers was obtained from the superintendent radiographer Mr Richard Cannon, who announced that the study was taking place in a departmental meeting. All subjects were given a written information sheet **(Appendix)** and assured that any information they gave would be strictly confidential.

To assess eating disorder severity all women completed the Eating Attitudes Test (EAT 26)**(Appendix)**. A score of less than 20 for women in the control group was considered to indicate that the radiographer had no evidence of an eating disorder. The prevalence of urinary symptoms in each group was determined using the King's Health Questionnaire, which was completed in private **(Appendix)**. Each bladder symptom was recorded as mild, moderate or severe by the subject, with absence of a response indicating that the woman did not have that urinary complaint. These answers were then converted into numerical scores of 0, 1, 2 or 3 allowing a mean score for each symptom and group to be calculated.

An assessment of each woman's menstrual pattern was made and the duration of amenorrhoea, if present, recorded. Details of any co-existent medical problems and medications were sought.

Body Mass Index (BMI) was calculated and a mid-stream sample of urine (MSU) sent for microscopy and culture. As described in **Chapter eight,** urinary tract infection was diagnosed when there was a pure growth of $>10^5$organisms / ml. Serum was taken on the same day that the questionnaires were completed and analysed for oestradiol, luteinizing hormone, follicle stimulating hormone, thyroid stimulating hormone and prolactin levels.

10.5.5 Statistical analysis

The data were analysed using the statistical package SPSS (version 8.0 for windows). The prevalence of urinary symptoms in each group was compared using the Chi-squared test. As information was sought about the prevalence of nine different urinary symptoms, there was a high probability of finding a significant difference between the groups just by chance. In view of the multiple comparisons a correction in the level of significance was made using the Bonferroni method ($P < 0.05 / 9 = 0.006$).

The quality of life data was not normally distributed and therefore analysed using the non-parametric Mann-Whitney test.

Logistic regression analysis is useful for trying to predict the presence or absence of a characteristic or outcome based on a set of predictor variables. This test was therefore used to assess the association between markers of oestrogen deficiency and the most common urinary symptoms.

10.6. RESULTS

10.6.1 Demographic data

A total of 55 women were recruited over a 4-month period. The study population comprised 30 women with eating disorders who were currently In-patients at the Royal Bethlam Hospital; 28 women had a diagnosis of severe anorexia nervosa and 2 women had severe bulimia nervosa. The median duration of time from diagnosis of an eating disorder was 7.4 years (IQR 3 - 9 years). 25 radiographers working at King's College Hospital agreed to act as controls.

None of the women with eating disorders refused participation but two of the radiographers who were approached were unable to take part; one did not wish to have blood taken and the other was eight weeks pregnant. The demographic details of each group are shown in **Table 10.1.**. The distribution of EAT 26 scores is demonstrated in **Figure 10.1.** and BMI in **Figure 10.2.**.

	EATING DISORDERS (n = 30)	CONTROLS (n = 25)
Mean age (years) (SD)	26.6 (7.3)	26.8 (4.7)
Number Parous	2 (6.6%)	2 (8%)
Number using COC	0 (0%)	12 (48%)
Median EAT 26 score (IQR)	52 (45-60)	3 (1-5)
Median Body Mass Index (IQR)	15.6 (14.9-17.8)	23.0 (20.7-25.0)

Table 10.1.: The baseline demographic details of the study population.

Figure 10.1.: The distribution of EAT 26 scores of the study population.

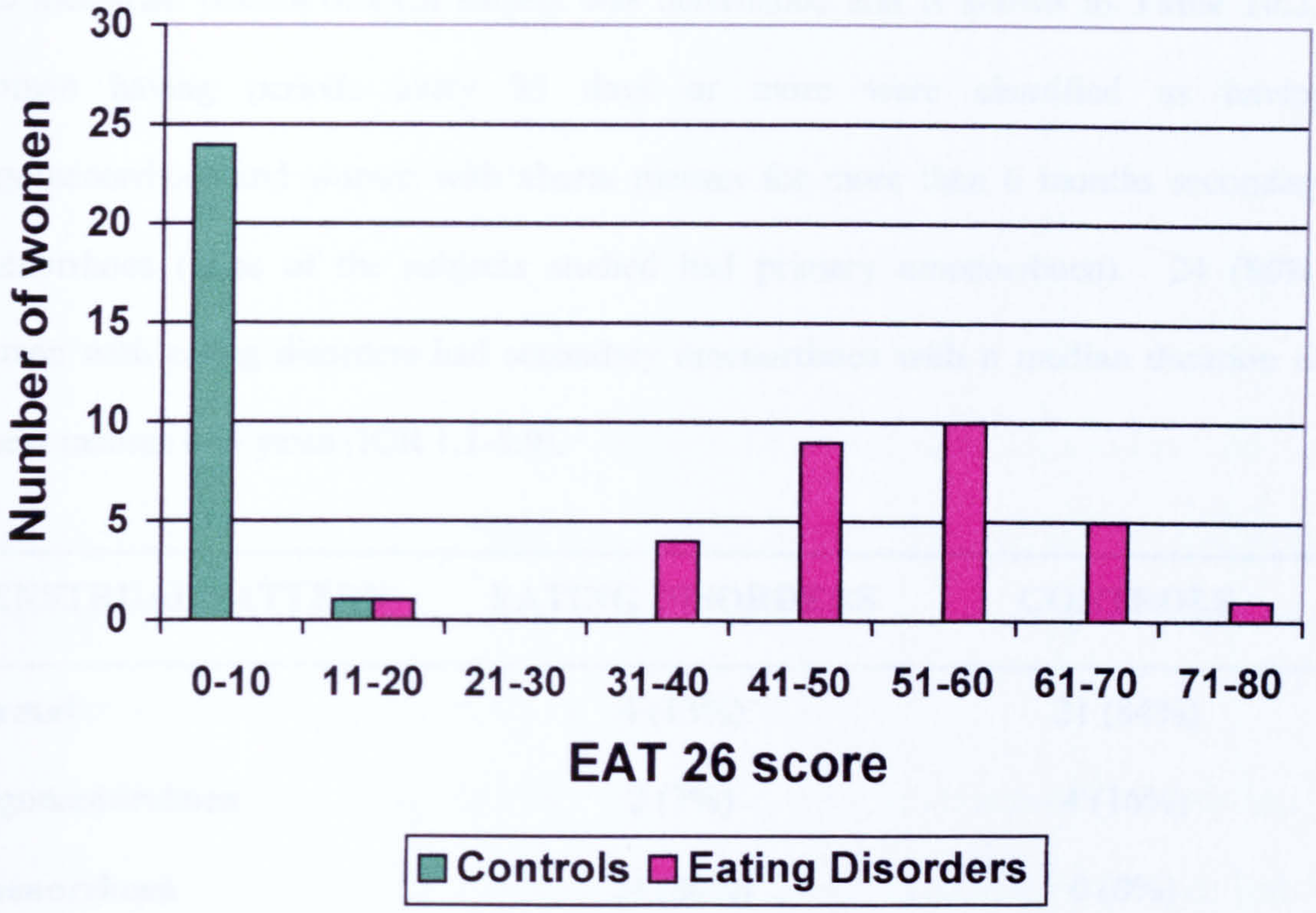
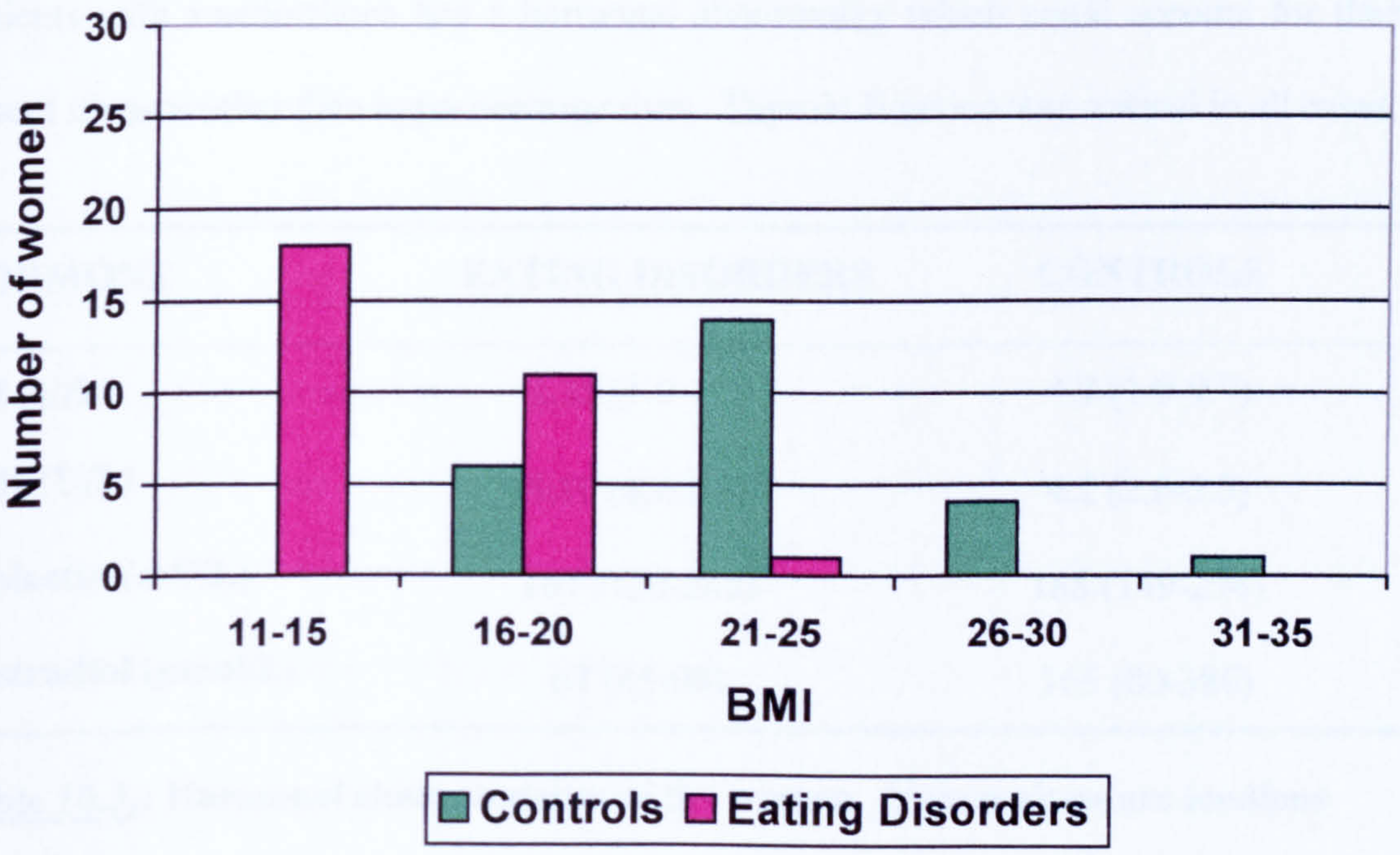


Figure 10.2.: The distribution of Body Mass Index measurements of the study population.



10.6.2 Hormonal Profile

The menstrual pattern of each subject was determined and is shown in **Table 10.2.**. Women having periods every 35 days or more were classified as having oligomenorrhoea and women with absent menses for more than 6 months secondary amenorrhoea (none of the subjects studied had primary amenorrhoea). 24 (80%) women with eating disorders had secondary amenorrhoea with a median duration of absent menses of 3 years (IQR 1.1-5.9).

MENSTRUAL PATTERN	EATING DISORDERS	CONTROLS
Normal	4 (13%)	21 (84%)
Oligomenorrhoea	2 (7%)	4 (16%)
Amenorrhoea	24 (80%)	0 (0%)

Table 10.2.: The menstrual pattern of the study population.

The results of the hormonal assays are shown in **Table 10.3.**. None of the patients with amenorrhoea had a hormonal abnormality which could account for their absent menses other than hypo-oestrogenism. Thyroid function was normal in all cases.

HORMONE	EATING DISORDERS	CONTROLS
LH (U/L)	1.35 (1.0-4.0)	4.7 (1.9-9.7)
FSH (U/L)	5.10 (4.0-6.3)	4.2 (2.0-5.3)
Prolactin (mU/L)	167 (130-240)	188 (149-294)
Oestradiol (pmol/L)	67 (45-98)	165 (80-380)

Table 10.3.: Hormonal characteristics of the women. Values given are medians (interquartile range).

10.6.3 Urinary tract infection

1 (3%) woman in the eating disorder group had a positive urine culture and this grew E. Coli. 2 (8%) women in the control group had an infected MSU sample. In one there was a positive culture of E. Coli and in the other Klebsiella.

10.6.4 Coexistent illnesses and Medication

6 (20%) women with an eating disorder had been diagnosed as having osteoporosis but none had a history of associated fractures. 1 (3%) woman had a history of angina for which she took GTN spray but no other cardiac medications. None of the women in the control group had a history of significant illness or surgery.

17 (57%) of the eating disorders group were using medication; 9 women were taking Fybogel for constipation, 1 women was using Ferrous sulphate for anaemia and 7 women were prescribed antidepressants. Only 3 (12%) women in the control group were taking medication at the time of the study; one was using Mebeverine for irritable bowel syndrome and the other two used inhalers for mild asthma.

10.6.5 Prevalence of urinary symptoms

All women in the study completed the King's Health Questionnaire. There was a highly significant difference in the overall prevalence of urinary symptoms between the two populations. In the eating disorder group 28/30 (93%) women complained of one or more urinary symptom compared to only 9/25 (36%) women in the control group (P=0.0001). The prevalence of each urinary symptom is detailed in **Table 10.4.**, with the most common shown in **Figure 10.3.**.

SYMPTOM	EATING DISORDERS (n=30)	CONTROLS (n=25)	SIGNIFICANCE
Frequency	26 (87)	6 (24)	**P = 0.00002**
Nocturia	25 (83)	7 (28)	**P = 0.00018**
Urgency	17 (57)	3 (12)	**P = 0.00224**
Urge incontinence	13 (43)	1 (4)	**P = 0.00317**
Stress incontinence	13 (43)	1 (4)	**P = 0.00317**
Nocturnal enuresis	6 (20)	1 (4)	P = 0.189
Intercourse incontinence	2 (7)	1 (4)	P = 0.08713
Recurrent infections	9 (30)	2 (8)	P = 0.08713
Bladder pain	8 (27)	0 (0)	P = 0.00633

Table 10.4.: The prevalence of urinary symptoms in the control group and women with eating disorders. Values given are n (%). The difference in the prevalence of bladder pain is not highlighted as significant in view of the Bonferroni correction.

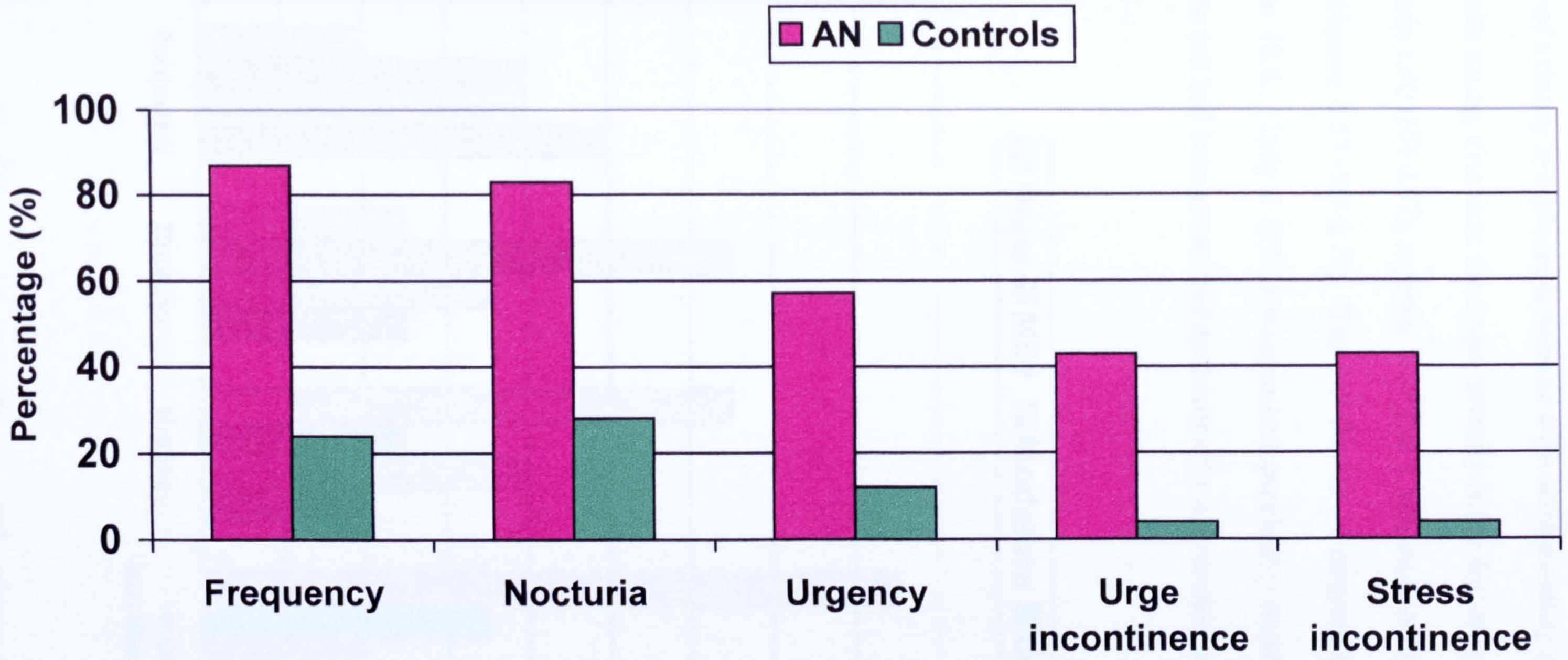


Figure 10.3.: The prevalence of the most commonly reported urinary symptoms in the women with eating disorders and the control group.

10.6.6 Severity of urinary symptoms in women with severe eating disorders

In the women with eating disorders the mean severity score for urinary frequency was 1.80 (SD 1.06), nocturia 1.40 (SD 0.97), urgency 1.10 (SD 1.12), urge incontinence 0.70 (SD 0.95) and stress incontinence 0.57 (SD 0.73). The distribution of responses for these symptoms is shown in **Figure 10.4.**. Only 4 (13%) women had previously received treatment for their urinary symptoms (all had been prescribed antibiotics for a presumed urinary tract infection).

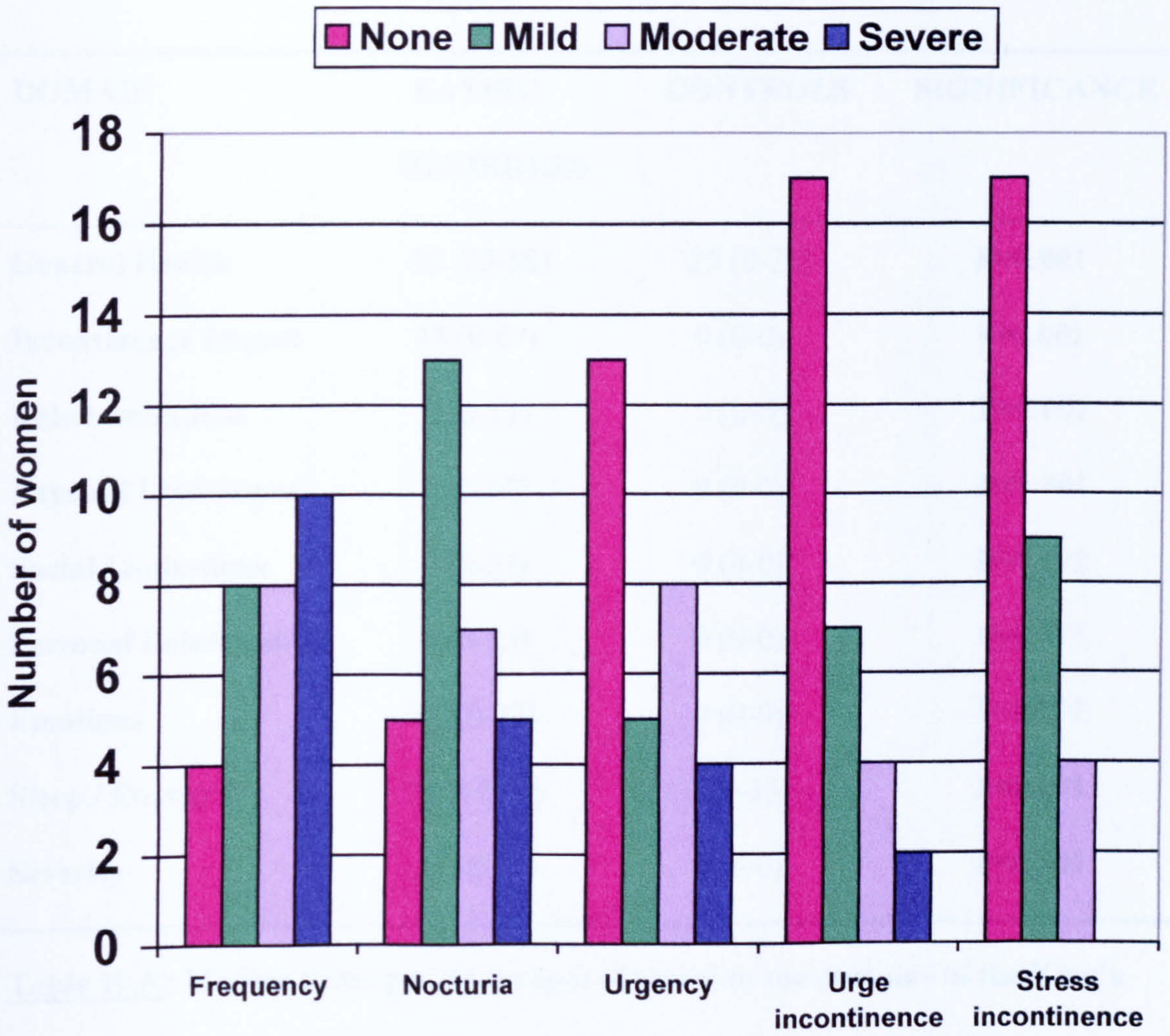


Figure 10.4.: The severity of the most commonly reported urinary symptoms in the women with eating disorders.

10.6.7. Impact of urinary symptoms on quality of life.

The King's Health Questionnaire was used to assess the impact of the women's urinary symptoms on their quality of life. There was a significant difference in the scores between each study group in all of the domains except social limitations (possibly because the women with an eating disorder were hospital In-patients) and personal relationships (probably because few of the women with an eating disorder had a partner). The effect on quality of life is shown in **Table 10.5.** and **Figure 10.5.**.

DOMAIN	EATING DISORDERS	CONTROLS	SIGNIFICANCE
General Health	50 (25-50)	25 (0-25)	**P=0.001**
Incontinence Impact	33 (0-67)	0 (0-0)	**P=0.001**
Role Limitations	0 (0-17)	0 (0-0)	**P=0.001**
Physical Limitations	0 (0-33)	0 (0-0)	**P<0.001**
Social Limitations	0 (0-21)	0 (0-0)	P=0.192
Personal Relationships	0 (0-13)	0 (0-0)	P=0.571
Emotions	11 (0-22)	0 (0-0)	**P<0.001**
Sleep / Energy	33 (17-50)	0 (0-33)	**P<0.001**
Severity	25 (8-42)	0 (0-0)	**P<0.001**

Table 10.5.: Median (interquartile range) of scores in the domains of the King's Health Questionnaire. Differences in the groups analysed using the Mann-Whitney test.

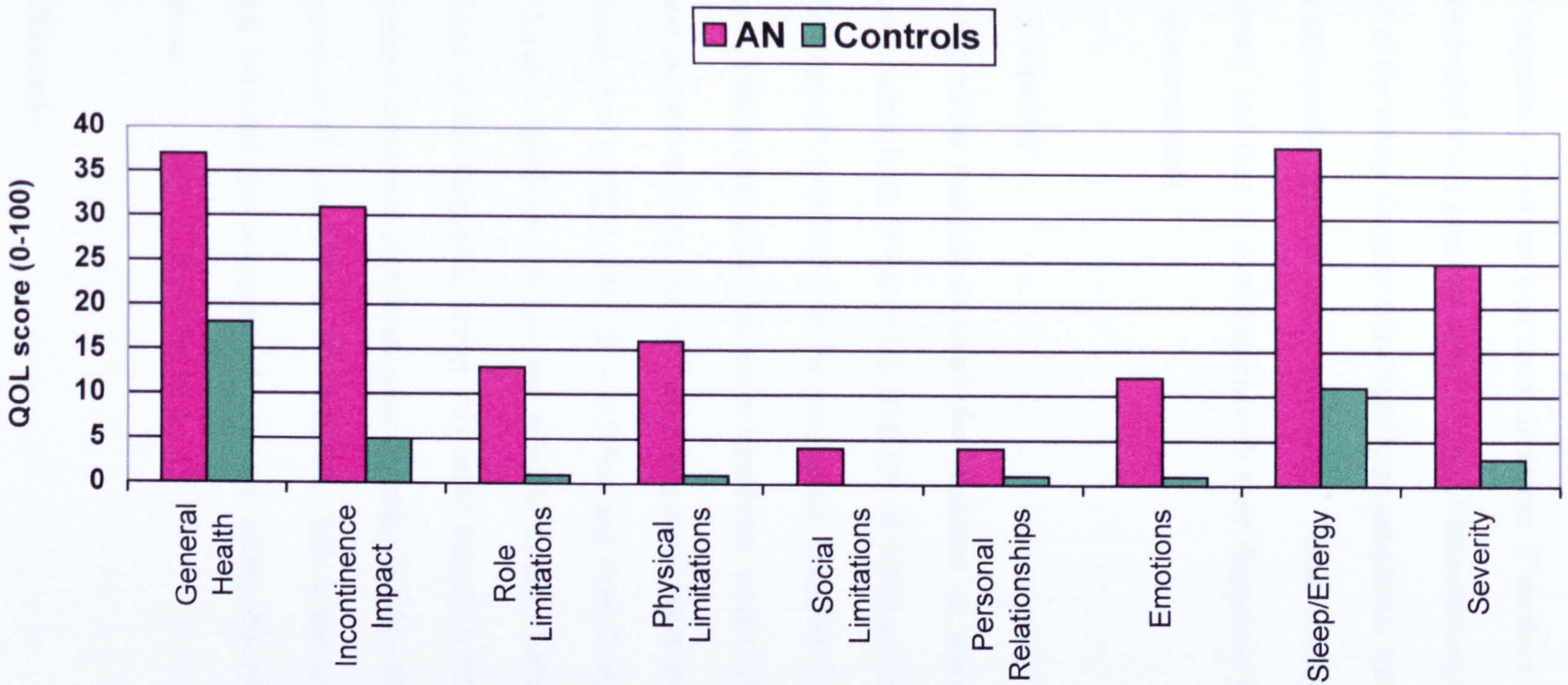


Figure 10.5.: Mean scores in each of the domains of the King's Health Questionnaire for each study group.

10.6.8 Role of oestrogen deficiency in the aetiology of urinary symptoms

Logistic regression analysis was used to assess if markers of oestrogen deficiency (serum oestradiol level, presence and duration of amenorrhoea), BMI and the time from diagnosis of the eating disorder were significant prognostic variables for the presence of the most commonly reported urinary symptoms. These variables were initially assessed independently and then in combination with their diagnostic group (eating disorder or control) as a covariable.

10.6.8.1. Frequency

Logistic regression analysis revealed the presence of amenorrhoea (P = 0.0047), duration of amenorrhoea (P = 0.0445), BMI (P = 0.0006) and time from diagnosis of an eating disorder (P = 0.0391) to be prognostic variables for the presence urinary frequency. Serum oestradiol was not a significant marker (P = 0.0527). However, when these factors were assessed with their diagnostic group as a covariable duration of amenorrhoea (P = 0.7225), BMI (P = 0.5960) and time from diagnosis (P = 0.7225) were no longer significant. It was not possible to tell which out of the presence of amenorrhoea or the diagnostic group was more directly related to urinary frequency because neither factor was significant after adjusting for the other (diagnostic group P = 0.8104, presence of amenorrhoea P = 0.8351). This is not surprising given the close association between the diagnosis of a severe eating disorder and the presence of amenorrhoea.

10.6.8.2. Nocturia

The presence of amenorrhoea (P = 0.0021) and BMI (P = 0.0015) initially appeared to be prognostic factors for the symptom of nocturia while duration of amenorrhoea (P =

0.0559), time from diagnosis of an eating disorder (P = 0.730) and serum oestradiol level (P = 0.420) did not. However, when analysed in combination with the diagnostic groups neither of these markers was significant. It would therefore appear that amenorrhoea and low BMI are proxies for the presence of an eating disorder when predicting if a woman will have nocturia.

10.6.8.3. Urgency

The presence of amenorrhoea (P = 0.0095) and time from diagnosis of an eating disorder (P = 0.0149) both initially appeared to be prognostic factors for the presence of urgency while duration of amenorrhoea (P = 0.0635), BMI (P = 0.138) and serum oestradiol level (P = 0.2710) did not. However, when analysed in combination with diagnostic group neither of these markers was significant. As with nocturia, other variables were simply proxies for the presence of an eating disorder when predicting if a woman had urinary urgency.

10.6.8.4. Urge incontinence

The presence of amenorrhoea (P = 0.0277), duration of amenorrhoea (P = 0.0235), BMI (P = 0.0083) and time from diagnosis of an eating disorder (P = 0.0092) all initially appeared to be prognostic variables for the prediction of urinary urge incontinence while serum oestradiol level was not (P = 0.0924). However, when these markers were analysed in combination with the diagnostic group none remained significant. It would therefore appear again that these variables were proxies for the presence of an eating disorder when predicting if a woman had urge incontinence.

10.6.8.5. Stress incontinence

Logistic regression analysis initially revealed only BMI to be a significant factor in predicting if a woman in the study complained of stress incontinence (P = 0.0209), but this was not independent of the diagnosis of an eating disorder (P = 0.6994). None of the other variables assessed, including parity, predicted if a woman would complain of this symptom.

10.7. DISCUSSION

10.7.1 Study design and recruitment of subjects

A number of epidemiological studies have implicated the menopause in the pathophysiology of urinary symptoms. However, it is uncertain how much of this effect is secondary to the ageing process and how much is due to oestrogen deficiency. The primary objective of this study was therefore to evaluate the urinary complaints of a group of young oestrogen deficient women, in whom the effects of ageing were likely to be less significant.

Several possible groups were considered when designing this study. Firstly, patients with premature ovarian failure. This is a relatively rare condition and most women are started on hormone replacement therapy almost immediately following diagnosis, making recruitment of a large sample of patients difficult. Secondly, women undergoing down-regulation with gonadotrophin analogues for endometriosis or fibroids, or as part of infertility treatment. However, in this group the duration of oestrogen deficiency is usually relatively short and urogenital symptoms may be influenced by other pelvic pathology. Therefore, the third option of studying women with severe eating disorders was selected. As outlined in **Chapter seven** this condition

is associated with anovulation and, as a consequence, the effects of oestrogen deficiency including amenorrhoea and osteoporosis.

After discussion with the colleagues in the eating disorders unit at the Royal Bethlam Hospital women with anorexia nervosa or bulimia nervosa, who were being treated as Inpatients, were recruited. These women certainly had evidence of prolonged, severe oestrogen deficiency. For example, the median serum oestradiol level at only 67 pmol/L was within the postmenopausal range, 87% had either oligomenorrhoea or amenorrhoea, and 20% had osteoporosis. The control group of radiographers was chosen as the women were likely to be of comparable age to the above study population; in fact both groups had a mean age of 26 years. However, they were shown different to the women with eating disorders in a number of important respects. Their median BMI was within the normal range, 84% had a regular menstrual cycle and none had evidence of an eating disorder on the EAT 26 questionnaire. The control subjects would therefore appear to represent a reasonable group for comparison.

The study was designed to assess differences in the prevalence of urinary complaints between the two groups. The King's Health Questionnaire proved to be extremely useful for this as it allowed both an evaluation of the severity of different urinary symptoms and also their impact on the quality of life of the patient. It was hoped that women in the eating disorder group would be prepared to undergo urodynamic investigation to try an identify any underlying functional abnormalities. Unfortunately, the medical staff in the eating disorders unit were not in favour of this as there were concerns that it may upset the women and effect the psychotherapy that most were undergoing. In addition, without exception the women themselves were not prepared to have investigations performed even though sometimes their urinary symptoms were reported as being severe.

10.7.2 Urinary symptoms in women with an eating disorder and their impact on Quality of Life

In common with our previous study (Boos et al 1999), women with eating disorders were shown to have a high prevalence of urinary symptoms. The small differences between the two studies were probably secondary to the different methods of collecting data – in the initial study a doctor administered questionnaire was used and this may account for the slightly lower prevalence of some of the symptoms. Following the menopause irritative urinary symptoms including frequency, urgency and urge incontinence occur commonly. This pattern was also found in our population of young women, providing further indirect evidence that the menopause and subsequent oestrogen deficiency are important in the pathogenesis of some urinary complaints. Interestingly, 43% of the women with an eating disorder admitted to having the symptom of stress incontinence, although only 2 (6.6%) were parous. It is possible that the underlying mechanism for this may be similar to that occurring in perimenopausal women. While the symptoms were mainly described as mild or moderate in their severity they were shown to have a significant impact on the quality of life of the women studied. However, despite this finding very few women had sought help or received treatment for their bladder problem in the past.

The background prevalence of urinary symptoms in the control group was similar to that found in previous epidemiological studies (Bungay et al 1980). This was reassuring as there was some concern that the radiographers would feel embarrassed to admit to any bladder complaints if they were not entirely happy that the study would be completely confidential. Therefore, this does not appear to have been a problem. It is almost always possible to criticise the choice of a control group and the one chosen in this study is no exception. Eating disorders are essentially a psychiatric problem which

are associated with a degree of stress and anxiety. It may therefore have been better to have used a control group of women with an anxiety state for comparison, although this group of women could perhaps have formed a third arm of the study. An anxiety score could then be calculated for each group and related to the prevalence of the urinary symptoms.

10.7.3 Is oestrogen deficiency the most likely cause of urinary symptoms in women with an eating disorder?

Patients with eating disorders differ from normal women in a number of important psychological and metabolic respects, as outlined in **Chapter seven.** There are therefore a number of possible reasons why this group of women may develop urinary symptoms. Many women with anorexia nervosa have psychosexual problems, possibly leading to an increased perception of the urogenital area. It could be speculated that this may produce concerns about bladder and vaginal symptoms which are in fact variations of normal. Some women with eating disorders increase their fluid intake to stop themselves feeling hungry while others use diuretics and laxatives to prevent weight gain. Alone or in combination these actions may lead to urinary frequency and nocturia. However, this does not appear to have been the cause of the increased prevalence of urinary symptoms in this study because the women were all living in a controlled environment where their oral intake of food was strictly monitored and fluid restricted to 1500ml / 24 hours. Although a number of women were taking antidepressants these were unlikely to be responsible for the high prevalence of irritative urinary complaints as these medications generally have an anticholinergic action, an effect which allows them to be used for treatment in women with abnormal detrusor activity. Their use may therefore have possibly reduced the prevalence of some symptoms.

The secondary objective of the study was to determine if measures of oestrogen deficiency were directly related to the presence of the most predominant urinary symptoms. Unfortunately, in this group of patients the diagnosis of an eating disorder and the presence of oestrogen deficiency were so closely linked that it was not possible to say which was the most important aetiological factor. The women assessed were all at the severe end of the disease spectrum and to investigate this question further it may be necessary to recruit women with a broader disease profile. An alternative approach would be to treat symptomatic women with oestrogen and see if they improved. The problem with this is that in general women with eating disorders do not like taking the combined oral contraceptive or other forms of oestrogen replacement as this treatment is associated with fluid retention and therefore mild weight gain. An alternative to limit this effect would be to give the oestrogen vaginally but overcoming the above concerns would probably still prove difficult.

It is possible to speculate that urinary symptoms may improve as a patient with an eating disorder responds to treatment, puts on weight and starts to ovulate again. However, anorexia nervosa tends to run a chronic, relapsing course and many women remain resistant to successful long-term treatment. Therefore, few women may return to normal and if they did it would still be difficult to be sure if a change in bladder symptoms was due an improvement in the patient's oestrogen status rather than for other reasons.

If the high prevalence of urinary symptoms in the women with eating disorders found in this study was secondary to oestrogen deficiency there are several possible underlying mechanisms (**Chapter six**). As well as a central action on oestrogen receptors in the brain, important peripheral changes in the urogenital tract itself may occur. For example, there may be a decrease in urethral pressure secondary to a

reduction in blood flow and cell cycle activity. Changes in connective tissues supports and pelvic floor muscle and collagen may also occur. Together these effects may be responsible for the unexpectedly high prevalence of stress incontinence found in the study. A fall in the sensory threshold of the bladder may also take place, making irritative symptoms of frequency and urgency more likely. Unfortunately, because this group of women are reluctant to undergo invasive testing identification of the exact underlying pathophysiological changes is likely to prove very difficult.

CHAPTER 11

THE EFFECT OF AGEING AND THE MENOPAUSE ON THE INCIDENCE OF BACTERIURIA

11.1. RATIONALE

Urinary tract infection occurs commonly in women following the menopause. However, it is uncertain if this effect is mainly due to the ageing process or secondary to changes in the urogenital tract which occur as a result of oestrogen deficiency. Following the menopause alterations in the vaginal flora are thought to place women at an increased risk of urinary tract infection. Unfortunately, randomised studies of oestrogen replacement therapy for prophylaxis against recurrent urinary tract infections have given conflicting results **(Chapter 8)**. The true effect of oestrogen deficiency on the prevalence of bacteriuria is therefore uncertain. To investigate this area further changes in the incidence of bacteriuria, and the type of infecting organisms, with respect to age were studied with the aim of detecting if the menopause had a significant effect.

11.2. NULL HYPOTHESIS

The following study was designed to test the null hypothesis that the menopause has no impact on the incidence of bacteriuria in women.

11.3. OBJECTIVES

11.3.1 Primary objective

The primary objective was to measure the incidence of bacteriuria in each age group with particular reference to changes occurring in the rate of infection at the time of the menopause and subsequent years.

11.3.2 Secondary objectives

The secondary objective was to document if changes occurred in the type of organisms infecting the urine with increasing age.

11.4. PATIENTS AND METHODS

11.4.1 Study population

All mid-stream urine (MSU) specimens sent to King's College Hospital from the community by General Practitioners (GP) in 1997 were assessed. Samples sent to the department of microbiology from the hospital wards, theatres or outpatient clinics were excluded. The study population therefore comprised the local population of community dwelling subjects.

11.4.2 Methods

On arrival at the King's College Hospital department of microbiology each MSU specimen was processed by Medical Laboratory Scientific Officers (MLSO). Analysis of the urine specimens was performed using an automated Mastascan system.

The principle of the Mastascan system is that a colour video camera measures reflected light levels from colonies of bacteria on agar media. A microcomputer then compares these digitised light levels with those obtained from appropriate controls and interprets the results depending upon a defined threshold. Signals from the colour tube in the camera are received by the computer as red, green and blue analogue signals. Circuitry within the computer changes these analogue signals to digital values which are then used to determine whether colour changes indicate a positive or negative reaction.

Provision is made in the computer software for the microbiologist to set the threshold level relating to the desired boundary between growth and no growth for a particular test. This threshold level is a percentage of the difference between the background (negative control) plate showing no growth and the control (positive) plate showing full growth. Differences in the colour reflected from colonies of bacteria are used to distinguish between different types of organism. Facilities are also available to

perform antibiotic susceptibility tests and antibiotic minimum inhibitory concentrations (MIC) determinants.

In the King's College Hospital department of microbiology the threshold level for diagnosing an infected urine sample is set at a pure growth of 10^5 organisms / ml. Lower counts are not considered to be indicative of a proven urinary tract infection. Cultures of more than one organism are coded as mixed growth and are thought to be indicative of poor sampling technique, perhaps associated with contamination from organisms colonising the perineum. They are therefore not regarded as demonstrating a urinary tract infection regardless of the presence of pus cells or white blood cells on microscopy. This means that specimens with a positive culture are reported as infected even if the white cell count is low, and conversely MSU samples with a culture below the positive threshold are reported as not infected even if the number of white cells in the urine is increased.

Following analysis of the MSU specimen by the Mastascan system each result is entered onto a computerised database and the information checked for accuracy by the MLSO. The database was set up in early 1996 and had therefore been running for over 6 months before this study commenced. There is a full time data systems manager working within the department of microbiology to ensure that any technical problems can be remedied almost immediately with no loss of data. Information entered onto the database comprises the patient's name, date of birth, sex, the result of the MSU sample and any relevant antibiotic sensitivities.

11.4.3 Statistical analysis

The data were analysed using the statistical package SPSS (version 8.0 for windows). I was assisted in the analysis of the results by Mr Richard Hooper, Lecturer in Medical Statistics at King's College Hospital. Logistic regression analysis was performed to investigate the relationship between age and the likelihood of having a positive (infected) MSU result. The results for men and women were compared. Changes in the rate of infection occurring around the time of the menopause were studied by looking for a non-linear (more specifically, a quadratic) relationship between age and the log odds of a positive result. Among positive MSU results from female subjects, the proportions due to particular infecting organisms were analysed in the same way to try and establish if the menopause led to a change in the bacterial flora of the infected urine.

The age of the menopause was defined as 50 years for the study population.

11.5. RESULTS

11.5.1 Number of MSU samples

16 314 MSU samples were sent from the community between 1.1.97 and 31.12.97 inclusive. Complete data was available for 15 392 (94%) of the specimens. Incomplete data was excluded from further analysis for the reasons outlined in **Table 11.1.**.

TYPE OF DATA	NUMBER OF MSU SAMPLES EXCLUDED
Missing age	337
Missing sex	561
Missing age and sex	24

Table 11.1.: Reasons MSU samples were excluded from analysis.

Of the 15 392 MSU samples with complete data, 11 811 (77%) were from women and 3 581 (23%) were from men. The age and sex distribution of the samples analysed is shown in **Figure 11.1.**.

Figure 11.1.: The age and sex distribution of MSU samples sent from the community to the department of microbiology in 1997.

11.5.2. Proportion of positive MSU samples

To examine the effect of age and sex on the likelihood of having a positive MSU result, the proportion of positive MSU results was calculated in each age group for both men and women. The proportion was calculated as follows:

$$\text{Proportion of positive results} = \frac{\text{Number of positive (infected) MSU samples}}{\text{Total number of MSU samples}}$$

Logistic regression analysis looking at the effects of age and sex found a significant *linear* effect of age (Chi-squared = 179.4, P<0.0001) which did not differ between males and females (interaction Chi-squared = 0.02, P = 0.88). However, there was a significant main effect of sex (Chi squared = 170.9, P<0.0001): a specimen taken from a woman was more likely to be positive than one taken from a man of the same age **(Figure 11.2.)**.

When *non-linear* effects of age were considered they were found to differ between men and women (interaction Chi-squared = 8.95, P = 0.003). In women, there was no evidence of any non-linear relationship between age and the log odds of a positive result (Chi-squared = 0.79, P = 0.37). A plot of the proportion of positive results did not suggest any departure from a linear relationship at or following the menopause.

In men, there was a significant *non-linear* relationship between age and the log odds of a positive result (Chi-squared = 14.4, P = 0.0001). Over the first 15-20 years of life the proportion of positive MSU results fell steadily but then increased thereafter with age.

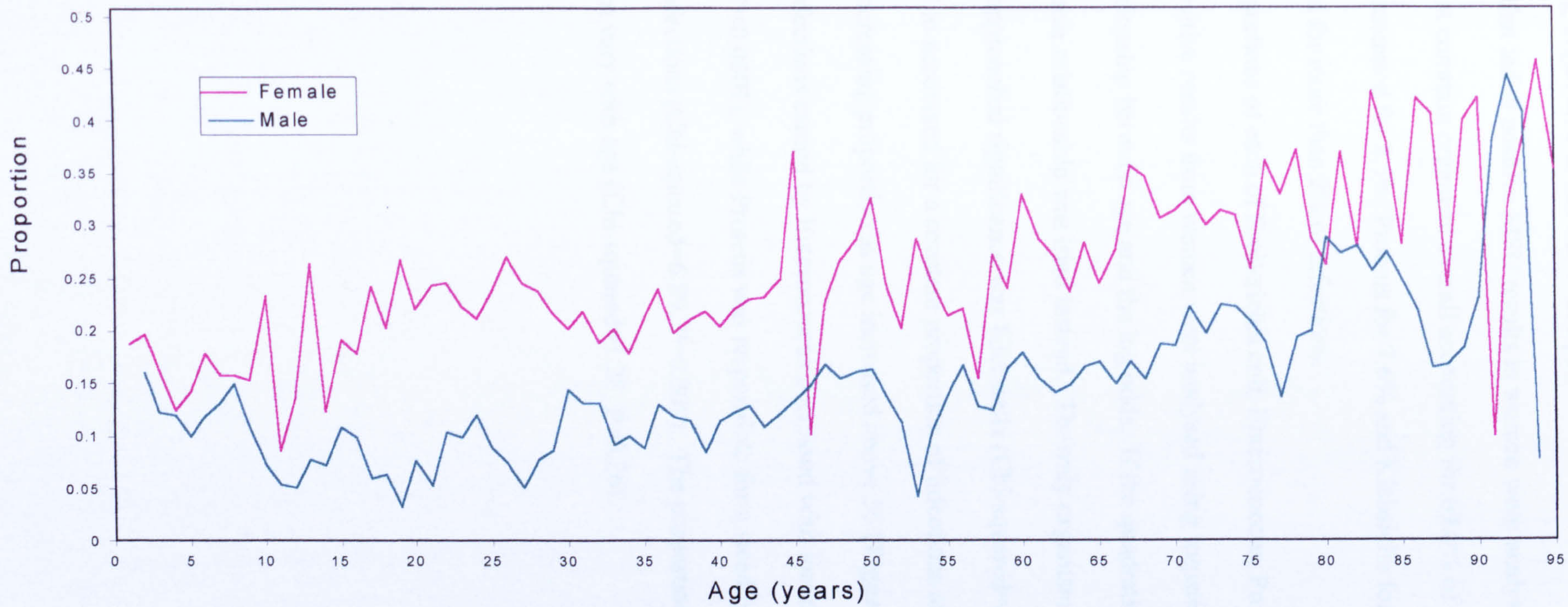
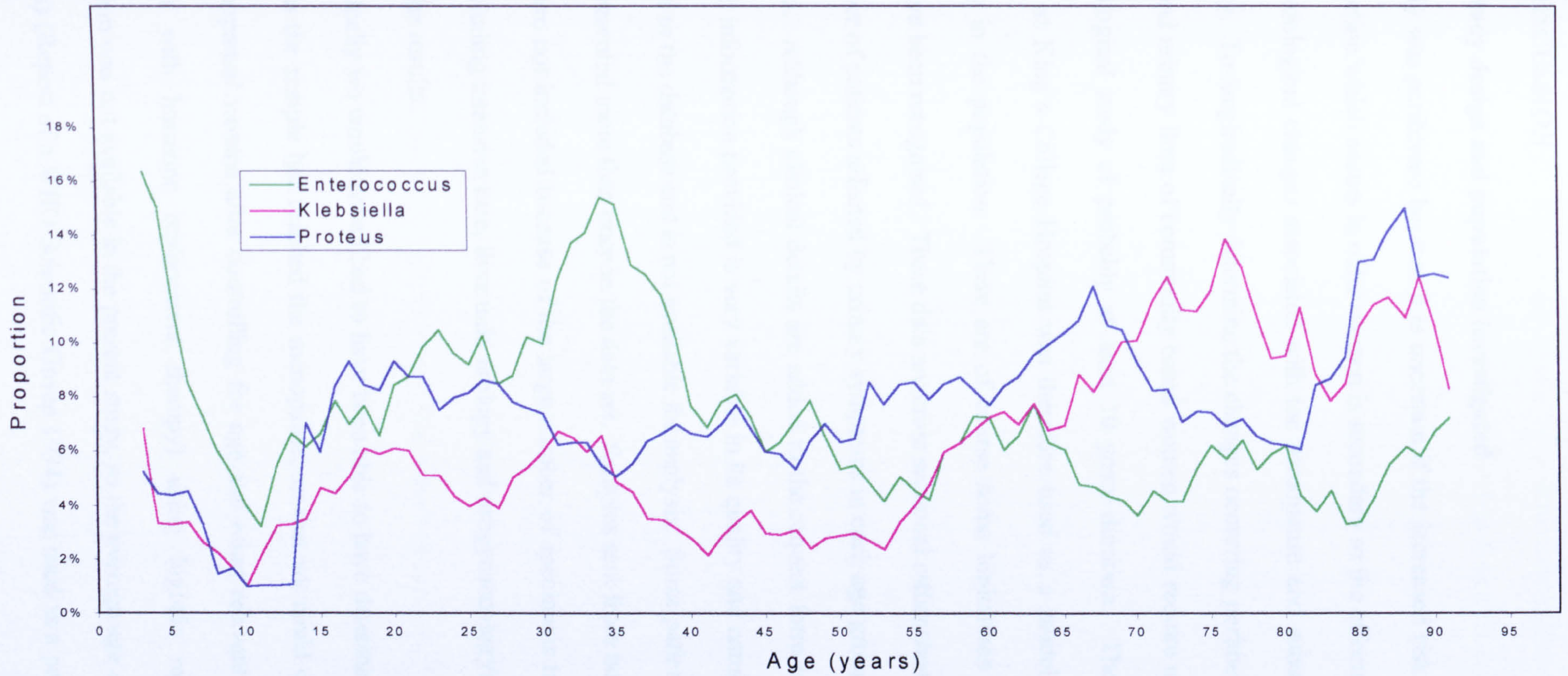


Figure11.2.: Proportion of samples that were positive, by subject's age. The proportions for females are calculated and plotted at each year of age. For males, from whom there were fewer samples, the proportion at a given age is calculated over a 3-year interval around that age.

11.5.3. Infecting organisms in the MSU samples

The organisms that led to positive MSU results in women were analysed. Escherichia coli was the most common organism overall accounting for 69.0% of infections, Enterococcus accounted for 8.5%, Proteus for 7.6% and Klebsiella for 6.1%. No other genus accounted for more than 2% of infections.

The proportions of each of Escherichia coli, Enterococcus, Proteus and Klebsiella in positive results from women were analysed using logistic regression to fit a quadratic relationship between age and the log odds. If the quadratic term was not significant, a linear relationship was tried instead. The only organism for which the quadratic term approached significance was Klebsiella (Chi-squared=3.60, P=0.058), which appeared to accounted for a constant proportion of infections at ages below 50, and a steadily increasing proportion as age increased above 50 (**Figure 11.3.**). The proportion of infections caused by Enterococcus decreased with increasing age (Chi-squared=28.0, P<0.0001), while Proteus was responsible for a steadily increasing proportion of infections (Chi-squared=6.89, P=0.009). The proportion of infections due to E. coli did not vary with age (Chi-squared=1.28, P=0.26).



<u>Figure 11.3.</u>: Proportions of the more common organisms in positive samples from female subjects. Overall, 69% of infections were caused by E. coli, and this proportion did not change significantly with age. This has been left off the graph in order to allow increased resolution at proportions below 20%.

11.6. DISCUSSION

11.6.1. Study design and population investigated

This study was performed because it is uncertain if the increased risk of lower urinary tract infection which occurs in older women is secondary to the effects of ageing or the pathophysiological changes associated with the menopause and subsequent oestrogen deficiency. To longitudinally determine the changes occurring perimenopausally in the vaginal and urinary flora of community based women would require a large, expensive epidemiological study of probably at least 10 years duration. The microbiological database at King's College Hospital was therefore used as a model for the changes occurring in the population. There are of course some limitations to this approach which have been recognised. These data are cross sectional rather than longitudinal and the number of patients affected by urinary symptoms in each age group is impossible to determine. Although clinical details are added to the request form in the majority of cases, the information provided is very variable in its quality and nature. It is therefore not added to the database and is not available for analysis. Some patients may also have been represented more than once in the data set. Samples sent from hospital clinics and wards were not included because of the large number of specimens taken in specialist units (including intensive care, liver unit, urology and urogynaecology) which may have skewed the results.

Ideally we would have liked to have been able to have determined whether each woman in the sample had reached the menopause, so that we could compare pre- and post-menopausal women after controlling for age and other relevant factors (such as treatment with hormone replacement therapy) using logistic regression. This information was not available in the present study, so the average age of the menopause (50 years) (Report of a WHO Scientific Group 1994) was used as a proxy for the onset

of oestrogen deficiency. The present uptake of hormone replacement therapy in the United Kingdom and elsewhere in Europe is probably less than 15% of women aged 40-65 (Barlow et al 1991, Wilkes & Meade 1991), with as many as 40% of women failing to complete 12 months of treatment even when there is a clear reason to do so (Ryan et al 1992). The use of oestrogen replacement in our study population is therefore unlikely to have had a significant effect on the results.

It can be seen from **Figure 11.1.** that the actual number of urine samples sent from each age group varied, with the highest number originating from women of childbearing age. To overcome this problem the proportion of samples infected for each age group was calculated. It was then possible to achieve the primary objective of the study and measure the incidence of bacteriuria in each age group with particular reference to changes occurring in the rate of infection at the time of the menopause and in subsequent years.

11.6.2. Role ageing and the menopause

If changes in the vaginal flora at or following the menopause were really responsible for the increased risk of bacteriuria as women get older, an acceleration in the number of positive MSU results with increasing age would have been expected, starting at the earliest ages of menopause (and furthermore this pattern would not have been repeated in male subjects). Instead what we found was a steady rate of increase in positive MSU results from females (and indeed from males) from early adulthood onwards. No significant change in the linear rate of increase in bacteriuria occurred around the age 50 years and in the subsequent postmenopausal years. This finding would suggest that while ageing is an important aetiological factor accounting for changes in the prevalence of bacteriuria (for reasons outlined in **Chapter eight**), in population terms

the menopause would appear to have little impact. This may in part explain the observation that while oestrogen has been shown to induce changes in vaginal flora which make urinary tract infection less likely, case controlled and randomised studies have not consistently shown this treatment to be better than placebo.

11.6.3. Menopause and organisms causing bacteriuria

The secondary objective of this study was to document if changes occurred in the type of organisms infecting the urine with increasing years. The most common infecting organism was E.Coli, which was present in 69% of infected samples from females and 49% of infected samples from males. The prevalence of E.Coli and the other organisms shown in **Figure 11.3.** was similar to that previously reported by Grüneberg (1994).

Logistic regression analysis showed only the proportion of infections secondary to Klebsiella to increase following the menopause. However, overall this organism accounts for relatively few infections and the clinical significance of this finding is therefore debatable. There was in fact a fall in the proportion of positive results due to an Enterococcus with increasing age in our sample, suggesting that colonisation of the vagina with bowel flora was not the main underlying cause for the increase in the rate of infection as women get older.

In summary, it can be concluded from this study that bacteriuria becomes more common in both men and women with increasing age. However, no significant changes appear to occur in the rate of infection or the infecting flora at the time of the menopause. It is therefore unlikely that pathophysiological changes in the urogenital tract which occur as a result of oestrogen deficiency following the menopause have a significant impact on the prevalence of bacteriuria in community dwelling women.

CHAPTER 12

A DOUBLE BLIND, PLACEBO CONTROLLED TRIAL ON THE EFFECTS OF 25MG OESTRADIOL IMPLANTS ON THE "URGE SYNDROME" IN POSTMENOPAUSAL WOMEN

12.1. RATIONALE

The background to this study is discussed in **Chapter five and Chapter six.** Oestrogen deficiency in postmenopausal women is thought to be an important factor in the aetiology of a number of lower urinary tract complaints including the "urge syndrome." This term is used to describe a clinical picture with a characteristic combination of urinary symptoms comprising frequency, nocturia, urgency and sometimes dysuria. Each urinary symptom may occur alone or in combination so the range of presentations of the "urge syndrome" and number of underlying diagnoses is large.

In some studies oestrogen replacement has been shown to improve urinary symptoms in postmenopausal women. However, even though a number of reports have been published in this area few are randomised, placebo controlled trials with subjective and objective outcome measures. In addition, most investigators have examined the efficacy of oral or vaginal oestrogen for genuine stress incontinence or urinary urgency using the relatively inactive oestrogen oestriol over a short follow up period. Parenteral administration of oestrogen using hormone implants avoids first pass metabolism in the liver, thereby ensuring a relatively high and constant serum oestradiol level compared to medication given orally. In addition, compliance with treatment can be assured. This double blind, placebo controlled study assesses the effect of 25mg oestradiol implants on the "urge syndrome" in postmenopausal women.

12.2. NULL HYPOTHESIS

This study was designed to test the hypothesis that low dose oestradiol implants have no impact on the "urge syndrome" in postmenopausal women.

12.3. OBJECTIVES

12.3.1. Primary objective

The primary objective was to study the efficacy of 25mg oestradiol implants for postmenopausal women with the "urge syndrome."

12.3.2. Secondary objectives

The secondary objective was to document the safety and tolerability of 25mg oestradiol implants used for treatment of the "urge syndrome" in postmenopausal women.

12.4. STUDY DESIGN

The study performed was a double blind, placebo controlled trial in one centre. The subjects were randomly allocated into one of two groups:

1) 25mg pure crystalline 17ß-oestradiol implant.
2) Placebo implant (implantation procedure performed but no implant given).

This design was chosen because it provides the most appropriate method of assessment of this therapeutic regimen. Appropriate randomisation ensured that any differences in the characteristics of the patients in each arm of the trial occurred by chance alone. Blinding of myself and the patients to the treatment given ensured that all assessments were unbiased.

12.5. POWER CALCULATION

Previous experience of recruitment to this type of study suggested we could not expect to recruit more than 60 subjects over a two and a half year period. With a cure rate in the placebo group of 25% this would give us 80% power at the 5% significance level to detect a group difference if the cure rate in the oestradiol group was 60% or more, though we recognised that at more realistic effect sizes the power would be reduced.

12.6. PATIENTS AND METHODS

12.6.1 Study population

Women diagnosed with the "urge syndrome" were recruited from the urodynamic clinic and urogynaecology outpatient clinic at King's College Hospital. Information about the trial was provided orally and using a written information sheet **(Appendix)**. Written informed consent was obtained prior to inclusion and signed by the patients and myself **(Appendix)**.

12.6.2. Inclusion criteria

The women enrolled in the trial fulfilled the following inclusion criteria:

1. Women had absent periods for at least 12 months, or if hysterectomised had a serum oestradiol level of less than 150 pmol/L.
2. The patients had a clinical diagnosis of the "urge syndrome."
3. Informed consent was given in writing.

12.6.3. Exclusion criteria:

The following exclusion criteria were used:

1. The patients were not taking any other treatment for the "urge syndrome" and in particular were not using anticholinergic medication or prophylactic antibiotics.
2. There was no history of diabetes mellitus or diabetes insipidus and the women were not taking diuretic therapy.
3. The women did not have a condition for which oestrogen therapy was contraindicated.
4. Patients had not received any hormone replacement therapy within 3 months of their enrolment into the trial, or had a previous implant or intramuscular hormone injection within the previous year.
5. There was no evidence of endometrial pathology. The women had either an endometrial thickness of 4mm or less on ultrasound or normal endometrium on histological examination following curettage.
6. The women did not have an infection or haematuria on an MSU sample.

12.6.4. Trial medication

The active medication used in the trial was a subcutaneous implant containing 25mg of pure crystalline 17ß-oestradiol. Randomisation was performed by Organon, who funded the study, on a 30 active: 30 placebo basis. A subject code was allocated to each implant and clearly labelled on the opaque box containing the trial medication. Women were assigned a code in numerical order of inclusion; the first subject received the first code, the second the next and so on. I did not have access to the randomisation codes, other than through the Emergency Drug Identification Record which was kept in the study folder.

The implant was administered by infiltration of the skin in the lower abdomen or buttock with 5-10ml of 1% lignocaine, and insertion of the implant into the subcutaneous tissue. A disposable fine bore trocar was used and no sutures were required. Women randomised to a placebo implant had identical packaging of the study medication but it did not contain an implant. They therefore had the same implantation procedure but no implant was given.

All the implantation procedures were performed by my registrar colleagues working in the department of urogynaecology. I was therefore blind to the whether the patient had received active or placebo treatment.

12.6.5 Subject assessment

The women recruited to the study all underwent a pre-trial assessment to ensure they met the inclusion and exclusion criteria. Potential subjects were fully informed about the study and gave written informed consent. The implantation procedure was performed as described above and follow up arranged for one month, three months and six months. Assessments and investigations were performed as outlined in **Table 12.1.**.

12.6.5.1. Medical history and physical examination

A detailed history was taken to include details of the patient's current urinary symptoms and previous medical complaints. Physical examination was performed with particular emphasis on excluding any contraindications to oestrogen therapy. Hypertension was excluded and clinical examination of the breasts made. Pelvic masses and significant urogenital prolapse which may have accounted for the woman's urinary symptoms were also excluded.

ASSESSMENT	BASELINE	1 MONTH	3 MONTHS	6 MONTHS
Physical examination	X			
Mid stream urine analysis	X	X	X	X
Serum oestradiol	X	X	X	X
Ultrasound endometrium	X	X	X	X
Questionnaires	X	X	X	X
Frequency volume chart	X	X	X	X
Uroflowmetry	X		X	
Videocystourethrography	X		X	
Urethral pressure profilometry	X		X	
Norethisterone administration				X

Table 12.1.: Flow chart of the assessments performed at baseline and each follow up visit. Norethisterone was given to all women with a uterus at their final visit.

12.6.5.2. Mid stream urine (MSU) specimen analysis

Urinary tract infection was excluded using the methods and criteria outlined in **Chapter eight.** Antibiotics were prescribed on the basis of culture and sensitivity results.

12.6.5.3. Serum oestradiol level

Serum was taken and assayed for oestradiol at each visit using the methods described in **Chapter five.**

12.6.5.4. Assessment of the endometrium

Women who had not previously undergone a hysterectomy had an assessment of their endometrial thickness made at baseline and each follow up visit using ultrasound. The screening measurements were performed by myself, and if the endometrial thickness was more than 4mm either an endometrium pipelle sample was taken or the patient referred for dilatation and curettage. All subsequent assessments of endometrial thickness were performed by research registrars working in the gynaecology ultrasound department at King's College Hospital. The results were given to me in a sealed envelope to ensure that I was not unblinded to the treatment given by seeing an endometrial response to an active implant. It was decided that no action should be taken if an endometrial thickness of more than 4mm developed during the study unless the patient complained of vaginal bleeding.

12.6.5.5. Questionnaires

Subjective assessments included a doctor administrated urinary symptoms questionnaire **(Appendix),** visual analogue score of symptom severity **(Appendix)** and the King's Health questionnaire **(Appendix).**

12.6.5.6. Frequency volume charts

A printed micturition chart in intervals of one hour (**Appendix**) was completed by the patient's at baseline and each follow up visit as described in **Chapter four.** The clinical efficacy evaluation was based on the following variables:

1) The mean number of micturitions/24h, calculated from complete days of recording.

2) The mean number of incontinence episodes/24h, calculated from complete days of recording.

3) The mean volume per micturition as determined by the formula:

$$\frac{\text{Total volume voided during all complete days of recording}}{\text{Total number of volume measurements}}$$

Only complete data for 24-hour days were included in the calculation of the number of micturitions, the number of incontinence episodes and the mean volume voided. Data were still included even if the result of an MSU sample taken at that visit was subsequently reported as showing a urinary tract infection.

12.6.5.7. Urodynamic assessment

I performed uroflowmetry, videocystourethrography and urethral pressure profilometry on each subject as described in **Chapter four** at baseline and after 3 months.

12.6.5.8. Adverse events

During each visit information on any adverse events experienced by the trial participants was sought. Upon entering the trial each subject was given a telephone

number which to use if they developed any problems. An adverse event was defined as any undesirable experience occurring to the subject during the trial period, whether or not it was related to the treatment given. A serious adverse event was defined as one which was life threatening, required hospitalisation or intervention to prevent permanent impairment. All other adverse events were regarded as non-serious.

12.6.5.9. Case report forms

All information about the trial participants was recorded in a case report form (CRF) which was available to representatives of Organon who monitored the visit every three months. Information was also recorded in the patient's hospital notes and the patient's general practitioner informed of entry into the study.

12.6.5.10 Final visit

At the end of the trial period all women with uterus were given a two-week course of norethisterone 5mg twice daily. If the patient had a withdrawal bleed this treatment was repeated on a monthly basis until the woman had two consecutive cycles without any vaginal loss.

12.6.5.11. Statistical analysis

All data collected in this study were recorded on or attached to the CRF's with the exception of the serum oestradiol results to ensure blinding was not compromised. Endometrial thickness results were kept in a sealed envelope as described earlier.

The data were entered onto a Microsoft Excel spreadsheet, checked for accuracy and then analysed using the statistical package SPSS (version 8.0 for windows). All data entry, processing and analysis was performed by myself. The change from

baseline of the urinary symptoms was analysed using the McNemar test with the Chi-squared test used for analysis between groups of categorical data. The numerical data were non-parametric data and therefore presented as medians (interquartile range) with comparisons from baseline made using the Wilcoxson signed rank sum test. The Mann-Whitney U test was used for comparisons between the groups.

12.7. RESULTS

The results of the first 30 women completing the study are presented. The first patient was recruited to the study in November 1996 and it was recognised at an early stage that the recruitment rate was falling short of that expected. Letters were sent to all staff working in the urogynaecology and obstetrics and gynaecology departments at King's College Hospital reminding them about the study and encouraging referral for entry. Local general practitioners and geriatricians were also contacted and offered very early assessment of any women that they felt might be suitable for the trial. A prominent notice was placed in the urodynamics clinic. Unfortunately none of these measures had a significant impact on patient referral or entry into the study. I have therefore analysed the results of the women who had completed the study when I left my post as a research registrar at the end of February 1999.

Eleven women who met the inclusion and exclusion criteria and were offered entry into the study indicated that they did not wish to take part. The main reasons given for this decision are shown in **Table 12.2.**.

REASON DID NOT PARTICIPATE	NUMBER OF WOMEN
Concerned about side effects	4 (36.3%)
Did not want a hormone implant	2 (18.2%)
Not prepared to receive a placebo	2 (18.2%)
Did not want HRT	1 (9.1%)
Did not want to take part in a study	1 (9.1%)
Other (patient unwell with shingles)	1 (9.1%)

Table 12.2.: Main reasons given by the women who did not wish to participate.

12.7.1 Demographic details

The demographic and baseline characteristics of the first 30 women completing the study are shown in **Table 12.3.**.

VARIABLE	OESTRADIOL IMPLANT (n=14)	PLACEBO (n=16)
Demographic variables		
Age at entry	66.3 (7.7)	66.6 (10.6)
Median parity (range)	2.0 (0-6)	2.5 (0-6)
Body Mass Index	26.5 (4.4)	29.4 (7.4)
Previous hysterectomy	3 (21%)	4 (25%)
Age at menarche	13.2 (2.0)	13.1 (2.3)
Age at menopause	48.9 (6.8)	49.4 (5.1)
Median duration of symptoms (IQR)	3.25 (1.6-6.5)	3.0 (2.5-4.0)
Symptoms began post-menopause	12 (86%)	15 (94%)
Characterisation of disease		
Number with abnormal detrusor activity on cystometry	4 (25%)	12 (75%)

Table 12.3.: Baseline demographic details of the women entered into the study. Values presented are means (SD) unless otherwise stated. Ages and duration of symptoms given in years.

12.7.2. Concurrent disease and concomitant therapy

12.7.2.1. Concurrent disease

28 (93%) women had at least one concurrent disease. The four most common concurrent diseases were arthritis (43%), polymyalgia rheumatica (7%), hypothyroidism (7%) and cataracts (7%). 1 (3%) woman had had a colposuspension seven years before entry to the study but none of the other women had undergone previous continence surgery.

12.7.2.2. Concurrent medication

As far as possible, concomitant medication was kept unchanged during the whole study period. Women with diabetes mellitus or diabetes insipidus and those taking anticholinergic therapy or diuretics were not included in the study. Concurrent medication was being taken by 15 (50%) women on entry to the study. The most commonly used medications were analgesics for arthritis (37%), prednisolone (10%), temazepam (10%), thyroxine (10%) and calcium channel blockers (7%).

Women with a proven urinary tract infection were treated with antibiotics for five days based on urine culture and sensitivity results.

12.7.3. Compliance, dropouts and protocol violations.

12.7.3.1. Compliance

One of the main advantages of this study over others that have used oestrogen for treatment of the "urge syndrome" is that by using a hormone implant compliance with treatment was assured. The implantation procedure was performed successfully and without difficulty in each case.

12.7.3.2. Dropouts

Two women given an oestradiol implant did not attend their final assessment but there were no other dropouts from the study. One woman did not arrive despite being given an appointment which she said was suitable for her. She also did not reply to two letters and unfortunately was not on the telephone. The other patient had a hysterectomy between the three-month and final visit because of heavy vaginal bleeding. This is reported in the serious adverse events.

12.7.3.3. Protocol violations

One woman given an oestradiol implant did not complete any frequency volume charts, as her eyesight was so poor that she could not read the gradations on a measuring jug. She in fact also did not attend her final assessment. One other patient given an oestradiol implant dropped out of the study and did not attend the final visit as outlined above. Otherwise the data collected was complete.

6 (43%) women given an oestradiol implant developed vaginal bleeding during the study (see adverse events) which unblinded me to the type of implant which had been given. In addition, they required treatment with progestogens which may have had some impact on their bladder function.

12.7.4. Mid stream urine specimens

Urinary tract infection was excluded on entry to the study by MSU culture. The number of positive MSU cultures at each follow up visit and overall are shown in **Table 12.4.**. As outlined in **Chapter eight,** women with a mixed growth of organisms on urine culture were treated as not having an infection, regardless of the white cell count in the urine.

There was no significant difference between the number of urinary tract infections found at each visit and overall between the two treatment groups. The use of antibiotics also did not differ significantly.

VISIT	OESTRADIOL	PLACEBO
1 MONTH	3/14 (21%)	5/16 (31%)
3 MONTHS	3/14 (21%)	0/16 (0%)
6 MONTHS	3/12 (25%)	8/16 (50%)
TOTAL	9/40 (23%)	13/48 (27%)

Comparison between the treatment groups using the Chi squared test.

Table 12.4.: The number (percentage) of positive (infected) mid stream urine samples at each follow up visit. The total indicates the number of positive samples/number of samples analysed.

12.7.5. Serum oestradiol levels

The serum oestradiol levels of the women in the study are shown below in **Table 12.5.**. At baseline the oestradiol levels in each treatment group were not statistically different. Following implantation, there was a highly significant increase in oestradiol level in the women given active treatment but not in those given placebo (P=0.001). The serum oestradiol level was therefore significantly higher in the active group at each assessment (P<0.0001).

VISIT	OESTRADIOL	PLACEBO
BASELINE	**44** (37-54)	**47** (30-55)
1 MONTH	**326** (245-382)	**50** (30-74)
3 MONTHS	**247** (183-354)	**46** (30-64)
6 MONTHS	**188** (143-253)	**36** (30-65)

Analysis of change in oestradiol levels from baseline using the Wilcoxson signed ranks test. Comparison of oestradiol levels between the groups at each visit using the Mann-Whitney U test.

Table 12.5.: Serum oestradiol levels (pmol/L). Values are given as medians (IQR).

12.7.6. Ultrasound measurements of endometrial thickness

The endometrial thickness measurements obtained using transvaginal ultrasound are presented below in **Table 12.6.**. At baseline all women had an endometrial thickness of less than 4mm. Following implantation, there was a highly significant increase in endometrial thickness in the women given active treatment but not in those given placebo ($P<0.05$). The endometrial thickness was therefore significantly greater in the active group at each assessment ($P<0.0001$).

VISIT	OESTRADIOL	PLACEBO
BASELINE	**3.0** (3.0-3.0)	**3.0** (2.0-3.0)
1 MONTH	**6.8** (5.0-8.3)	**2.1** (1.4-3.0)
3 MONTHS	**11.5** (9.9-17.8)	**2.7** (1.5-3.0)
6 MONTHS	**9.5** (7.0-13.8)	**3.0** (2.1-3.0)

Analysis of change in endometrial thickness from baseline using the Wilcoxson signed ranks test. Comparison of endometrial thickness between the groups at each visit using the Mann-Whitney U test.

Table 12.6.: Endometrial thickness measurements (mm). Values are given as medians (IQR)

12.7.7. Efficacy of 25mg oestradiol implants for treatment of the "urge syndrome"

12.7.7.1. Urinary symptom questionnaire

Data regarding each symptom were obtained by direct questioning using the urinary symptoms questionnaire (**Table 12.7.**). Cure was defined as the complete absence of a specific urinary symptom which was present on entry to the study. Two women from the oestradiol group did not attend the final assessment and this is represented by a change in the denominator.

There was an improvement in the symptom of urge incontinence in the women given an oestradiol implant at the three and six month assessments ($P<0.05$). However, there were no other significant changes and no differences between the two groups.

SYMPTOM	ENTRY	1/12	3/12	6/12	% CURED
Urgency					
Oestradiol	14/14	13/14	11/14	9/12	**25%**
Placebo	16/16	14/16	15/16	15/16	**6%**
Urge Incont					
Oestradiol	11/14	8/14	5/14 [a]	4/12 [a]	**44%**
Placebo	10/16	9/16	9/16	7/16	**30%**
Stress Incont					
Oestradiol	8/14	7/14	5/14	5/12	**29%**
Placebo	5/16	3/16	3/16	4/16	**20%**
Dysuria					
Oestradiol	5/14	3/14	2/14	1/12	**80%**
Placebo	3/16	4/16	2/16	2/16	**33%**

[a] $P<0.05$, McNemar test. Comparison of urinary symptoms from entry.

Table 12.7.: Number of women complaining of different urinary symptoms at entry and each assessment visit. Cure applies to absence of a symptom at the end of the study. This figure takes account of the initial symptoms of the women who did not attend for their final assessment.

12.7.7.2. King's Health Questionnaire

Quality of life was assessed at baseline and each follow up visit using the disease specific King's Health questionnaire. The results are presented in **Table 12.8.**. It can be seen there was virtually no change in the general health scores over the study period, providing further evidence of the validity and consistency of the questionnaire.

There were no significant changes in the quality of life scores in any of the domains in either the oestrogen or placebo groups. In addition, there were no trends towards improvement in any of the areas measured. It is therefore unlikely that even when 60 patients have completed the study that oestrogen will be shown to improve the quality of life of women with the "urge syndrome."

DOMAIN	ENTRY	1/12	3/12	6/12
General Health Perception				
Oestradiol	50 (25-50)	50 (25-50)	50 (19-75))	25 (25-50)
Placebo	50 (19-75)	50 (25-75)	50 (25-50))	25 (25-50)
Incontinence Impact				
Oestradiol	84 (67-100)	83 (50-92)	83 (50-92)	33 (33-67)
Placebo	67 (34-100)	67 (33-100)	67 (33-100)	33 (33-67)
Role Limitations				
Oestradiol	50 (33-84)	42 (17-67)	50 (33-67)	33 (17-67)
Placebo	50 (33-67)	50 (33-67)	33 (17-68)	33 (17-67)
Physical Limitations				
Oestradiol	50 (25-63)	42 (33-67)	33 (17-67)	50 (33-84)
Placebo	67 (33-84)	33 (17-67)	50 (21-67)	33 (17-67)
Social Limitations				
Oestradiol	33 (0-67)	33 (0-67)	22 (0-33)	22 (6-56)
Placebo	50 (25-58)	33 (0-67)	33 (0-67)	22 (0-56)
Personal Relationships				
Oestradiol	0 (0-33)	8.4 (0-33)	0 (0-33)	0 (0-25)
Placebo	0 (0-25)	0 (0-33)	0 (0-25)	0(0-25)
Emotions				
Oestradiol	56 (33-89)	44 (19-80)	33 (22-67)	33 (22-67)
Placebo	50 (33-84)	55 (33-89)	44 (22-78)	50 (21-67)
Sleep / Energy				
Oestradiol	50 (25-64)	50 (33-67)	50 (33-71)	50 (33-67)
Placebo	33 (22-67)	50 (33-71)	67 (33-83)	50 (33-71)
Severity Measures				
Oestradiol	42 (13-52)	38 (13-46)	50 (38-75)	50 (25-75)
Placebo	34 (17-50)	50 (38-75)	50 (25-73)	34 (17-50)

Comparison from baseline using the Wilcoxson signed ranks test. Comparison between groups using the Mann-Whitney U test.

Table 12.8.: King's Health questionnaire scores at each visit. Values given as medians (IQR).

12.7.7.3. Visual analogue scores

There was a significant improvement in the symptoms of frequency, nocturia and urgency in both groups over the study period. Urge incontinence also improved in women given oestradiol. It can be seen that overall there was a trend for the improvement to have started by the first follow up visit at one month and then continue until the end of the trial period. However, at no time were the scores of any of the symptoms statistically different between the two treatment groups. These results are presented in **Table 12.9.**.

VARIABLE	BASELINE	1/12	3/12	6/12
Frequency				
Oestradiol	**64.2** (56.3-72.1)	**47.8** (40.9-54.7) [a]	**48.1** (38.7-57.5)	**37.0** (28.6-45.4) [a]
Placebo	**69.6** (63.7-75.5)	**56.8** (50.3-63.3)	**47.0** (40.8-53.2) [b]	**54.0** (46.6-61.4) [a]
Nocturia				
Oestradiol	**55.1** (47.1-63.1)	**46.2** (38.1-54.1)	**43.9** (34.3-53.5)	**36.8** (28.2-45.4) [a]
Placebo	**70.3** (64.7-75.9)	**63.3** (55.6-71.0)	**47.8** (40.5-55.1) [a]	**47.0** (40.3-53.7) [a]
Urgency				
Oestradiol	**79.6** (75.3-83.9)	**54.6** (47.3-61.9) [a]	**45.2** (35.6-54.8) [a]	**34.4** (24.6-44.2) [a]
Placebo	**75.2** (71.2-79.2)	**52.3** (45.7-58.9) [a]	**34.6** (28.0-41.2) [b]	**47.5** (40.5-54.5) [b]
Urge Incontinence				
Oestradiol	**50.1** (40.8-59.4)	**29.2** (21.9-36.5)	**26.0** (17.5-34.5) [a]	**25.7** (16.7-34.7) [a]
Placebo	**32.1** (25.0-39.2)	**36.8** (28.5-45.1)	**21.6** (15.2-28.0)	**30.3** (21.9-39.1)

[a] $P<0.05$, Comparison with baseline using Wilcoxson signed ranks test
[b] $P<0.01$, Comparison with baseline using Wilcoxson signed ranks test

Table 12.9.: Visual analogue scores (0-100mm). Results presented as medians (IQR).

12.7.7.4. Frequency volume charts

Data obtained from the frequency volume charts is presented in **Table 12.10.** There were no significant differences between the treatment groups at baseline. After 3 months the median volume voided per micturition was significantly greater in the women given an oestradiol implant. After 6 months there was a statistically significant reduction in the mean number of micturitions/24 hours in the women given an oestradiol implant. However, there were no other statistically significant changes from the baseline values.

VARIABLE	BASELINE	1/12	3/12	6/12
Micturitions/24h				
Oestradiol	**10.2** (9-11)	**8.5** (8-10)	**10.0** (7-11)	**8.0** (6-11) [a]
Placebo	**8.3** (7-10)	**7.7** (7-11)	**8.5** (7-11)	**7.9** (7-10)
Volume voided/micturition				
Oestradiol	**165** (144-234)	**205** (147-232)	**217** (160-250) [b]	**186** (157-218)
Placebo	**147** (134-175)	**158** (119-200)	**170** (124-200)	**154** (112-198)
Incontinence episodes/24h				
Oestradiol	**1.3** (0-1.6)	**0.4** (0-1.9)	**0** (0-1.8)	**0** (0-0.5)
Placebo	**0** (0-1.6)	**0** (0-1.8)	**0** (0-1.7)	**0** (0-0.5)

[a] $P<0.05$, Comparison with baseline using Wilcoxson signed ranks test.
[b] $P<0.05$, Comparison between groups using Mann-Whitney U test.

Table 12.10.: Data obtained from the frequency volume charts at baseline and each follow up visit. Median values (IQR) are given.

12.7.7.5. Uroflowmetry and videocystourethrography

There were no significant differences in the urodynamic variables at baseline between each group and no statistically significant changes from baseline on follow-up assessment three months after entry (**Table 12.11.**). However, the women given an oestradiol implant had a higher median first sensation to void and larger median cystometric capacity than those given a placebo after three months of treatment.

ASSESSMENT	BASELINE	3/12
Uroflowmetry		
(a) Flow rate		
Oestradiol	**23** (18-25)	**20** (12-25)
Placebo	**15** (12-16)	**14** (10-18)
Videocystourethrography		
(b) 1st sensation		
Oestradiol	**175** (100-250)	**220** (150-300) [a]
Placebo	**150** (100-160)	**150** (102-150)
(c) Maximum capacity		
Oestradiol	**440** (350-500)	**463** (363-495) [a]
Placebo	**350** (300-400)	**320** (278-366)
(d) Pressure rise on filling		
Oestradiol	**10** (5-20)	**5** (5-19)
Placebo	**19** (10-29)	**19** (5-20)
(e) Volume P>15cm H_2O		
Oestradiol	**275** (175-360)	**250** (200-450)
Placebo	**290** (150-300)	**250** (110-250)

[a] P<0.05, Comparison between groups using Mann-Whitney U test.

Table 12.11.: Urodynamic variables at baseline and 3 months. Values given are medians (IQR). One woman given an oestradiol implant refused to have repeat urodynamics because of vaginal bleeding.

12.7.7.6. Urethral pressure profilometry

The urethral pressure profile was measured at baseline and again three months after implantation (**Figure 12.1.**). There were no significant changes in either the maximum urethral closure pressure (MUCP) or functional urethral length (FUL) in either group over the study period.

The pressure transmission ratio was calculated for each quartile of the urethral pressure profile. There were no significant changes following implantation and no significant differences between the groups at either assessment.

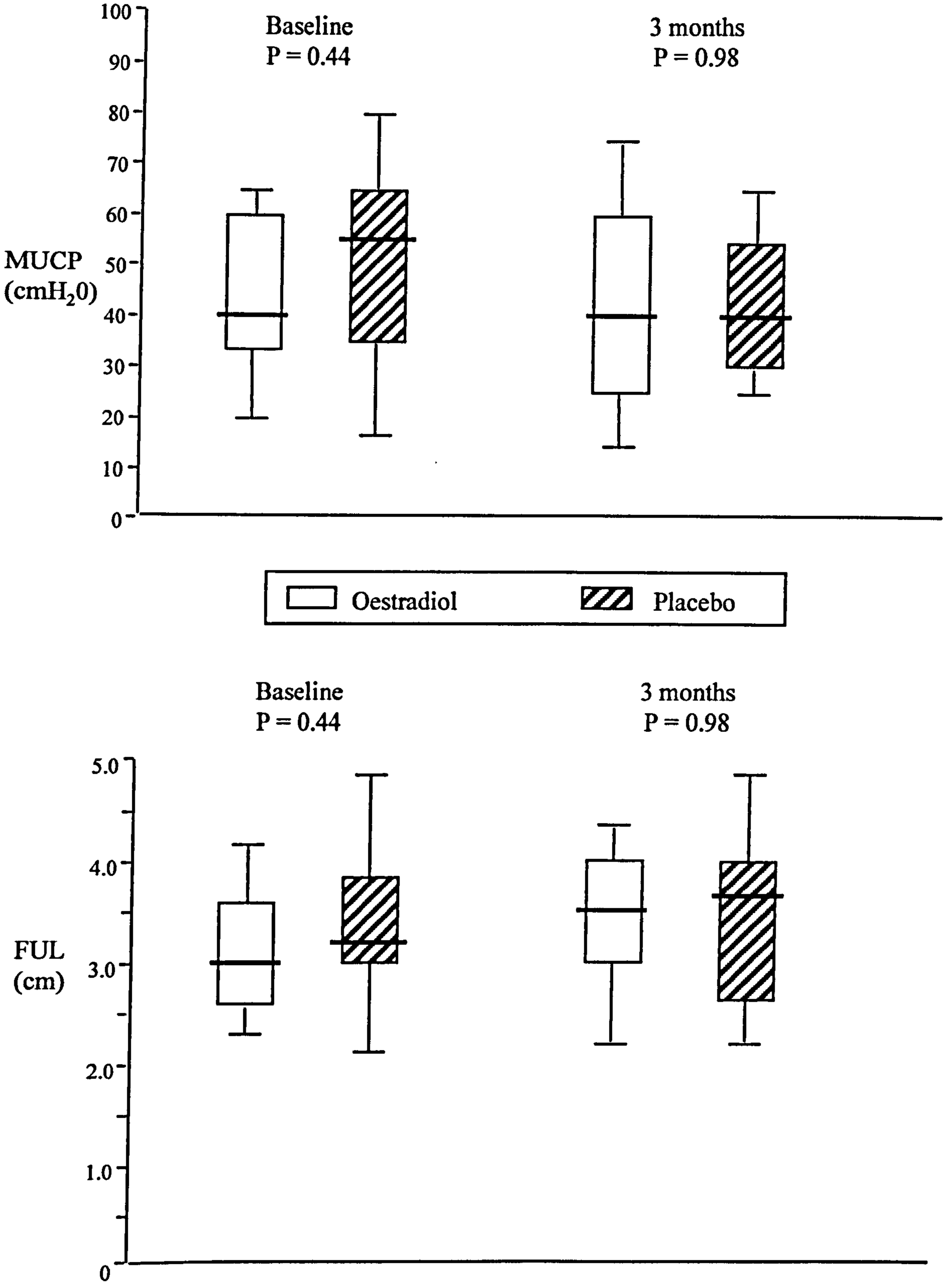


Figure 12.1.: Urethral pressure profile parameters. Median values, interquartile range and ranges shown. Comparison between the groups using the Mann Whitney U test.

12.7.8. Adverse events

12.7.8.1. Implantation procedure

There were no adverse events associated with the implantation procedure itself other than minor bruising which settled spontaneously within a few days.

12.7.8.2. Non-serious adverse events

None of the women given a placebo complained of any non-serious adverse events during the study period other than a proven urinary tract infection, the frequency of which is presented earlier. Of the patients given an oestradiol implant, 3 (21%) women complained of mild breast tenderness which was most uncomfortable in the first 4 weeks after implantation and then gradually settled. They were reassured and advised to wear a support bra. None felt that they required analgesia for this problem.

6/11 (55%) women with a uterus who were given an oestradiol implant developed vaginal bleeding during the study. This started 9-18 weeks after implantation and in each case was associated with thickened endometrium on ultrasound (range 9-20mm). The histology of the endometrial pipelles taken was reported as showing evidence of exogenous oestrogen administration but not hyperplasia or malignancy. The women were started on oral progestogens, but despite taking increasing doses the bleeding tended to occur intermittently throughout the study period, although with the exception of one of the patients (reported in the serious adverse events) it was generally light in nature.

12.7.8.3. Serious adverse events

One women given an oestradiol implant was admitted to another hospital with angina 4 months after implantation and underwent angioplasty. The team responsible for her

care apparently did not feel that her angina developed as a result of her treatment with oestrogen. She attended her final visit as planned.

One (9%) woman with a uterus who was given an oestradiol implant developed very heavy vaginal bleeding 18 weeks after entry into the study. On ultrasound the endometrium was thickened and cystic with a measurement of 20mm. An endometrial pipelle sample showed blood and only a few fragments of endometrium, which were insufficient for histological analysis. In view of the significant loss she was started on provera 50mg daily with arrangements made for repeat assessment the following week. However, as she felt the bleeding was getting heavier she was admitted to the ward for observation earlier than her planned appointment. Her haemoglobin was 12.5g/dl. A dilatation and curettage was performed under general anaesthetic. The uterus was found to be enlarged to 12-week size, although it was normal in size on entry to the study. The histology of the curettings was reported as showing: "small inactive endometrial glands and decidualized stroma consistent with exogenous hormone treatment. A dense acute inflammatory infiltrate is present associated with focal degenerative changes and necrosis. The features are those of necrotic decidualized stroma with secondary inflammatory changes. There is no evidence of malignancy."

In view of the enlarged uterus and continuing heavy bleeding following curettage, the patient was offered a vaginal hysterectomy by the team continuing with her care. This was performed uneventfully and she made a good post-operative recovery. The endometrial cavity contained white polypoid tissue measuring 2.5 x 1.5 x 0.6cm at maximum. The appearances on histology were identical to those of the endometrial curettings. There was again no evidence of hyperplasia or malignancy.

12.8. DISCUSSION

12.8.1. Study design and recruitment of subjects

Urogenital symptoms including those associated with the "urge syndrome" occur commonly following the menopause. It is therefore reasonable to assume that oestrogen supplementation may be useful for the treatment of postmenopausal urinary symptoms, particularly as the lower urinary tract has been shown to be sensitive to the effect of sex steroids. This study was designed to test the hypothesis that oestrogen replacement therapy given as an implant would be effective in the treatment of the "urge syndrome." In view of the known large placebo effect which has been demonstrated in previous research into this condition a double blind, placebo controlled randomised study was considered to be the most appropriate design for this trial. Several steps were taken to ensure that the patients and myself remained blinded to the type of treatment given. Firstly, the study medication was kept in sealed and coded boxes before the implantation procedure, which was performed by colleagues in the department of urogynaecology. Secondly, the results of the serum oestradiol measurements and ultrasound scans were kept separately until the patients had completed the trial. Unfortunately, 6 women in the study developed vaginal bleeding which effectively revealed that these patients were in the active treatment group (as it was very unlikely that any of these women would have been in the placebo arm of the study).

The rationale and safety of using unopposed oestradiol implants has been discussed in **Chapter five.** We chose to use 25mg oestradiol implants as this dose would hopefully provide an adequate therapeutic dose of oestrogen to treat the "urge syndrome" while keeping the effects on the endometrium to a minimum. By using an implant rather than other forms of oestrogen administration a relatively stable serum level of oestradiol was achieved and compliance was assured. The risk of a woman

developing endometrial carcinoma after six months of unopposed oestrogen therapy is extremely low with a relative risk of 0.6-1.4 (Grady et al 1995). Addition of a cyclical progestogen would have reduced the likelihood of the patients developing significant endometrial problems even further. However, this would have had the effect of inducing regular withdrawal bleeds, unblinding the study and reducing the acceptability of the treatment to the women. In addition, progestogens have been shown to have a largely detrimental effect on lower urinary tract symptoms and their use would have added a significant confounding factor which may have interfered with interpretation of the results of the study.

Recruiting women to the trial was difficult and slower than anticipated. This problem was also found by Cardozo and colleagues (1993b), who only managed to assess 64 women from 10 centres over an 18 month period, and Jackson and associates (1999) who also failed to enrol as many women as planned. There are a number of reasons why this may be the case. Although there are few studies showing that oestrogen is efficacious for the treatment of postmenopausal urgency, it is widely held view amongst general practitioners and some gynaecologists that it can be of benefit in this situation. It may be therefore that a large number of women in the community will have presented with symptoms of the "urge syndrome" and have been successfully treated without the need for referral to hospital. This would reduce the number of women with this condition seen in a hospital setting and possibly mean that the majority of patients assessed in our clinic were at the more severe end of the disease spectrum. In addition, although overall less than 15% of women use HRT in the community (Barlow 1991, Wilkes 1991) surprisingly as many as 40% of the postmenopausal women referred with urinary symptoms had already used oestrogen replacement (**Section 9.5.5.**). In contrast to some other studies only women who were definitely

oestrogen deficient and had not been taking HRT recently were sought, as it was felt that these women were most likely to respond to treatment. Perhaps the inclusion and exclusion criteria for entry into the study were also too rigid. However, it was important to make sure that the patients studied did not have other underlying conditions and were not taking medication which may have accounted for their symptoms.

The other main obstacle to recruitment was the fact that approximately 50% of those patients who did not want to take part in the study indicated that this was because they were unwilling to take HRT, have an implant or were worried about the side effects of oestrogen. The risk of developing carcinoma of the breast associated with HRT does not start to increase until women have had 10 years of treatment. However, this disease is clearly of great concern to many women and therefore use of oestrogen replacement therapy may not be welcome, particularly if alternative treatments are available.

12.8.2 Efficacy of 25mg oestradiol implants for the treatment of the "urge syndrome"

The study population appear to represent a typical group of postmenopausal women with the "urge syndrome." The mean age of the women was 66 years, with 90% of the patients developing symptoms following the menopause. In common with epidemiological studies of urogenital problems the symptoms were also characteristically of long duration (Thomas et al 1980, Barlow et al 1997). The concurrent illnesses and medications being taken were compatible with the age group of the study population. In addition, the incidence of bacteriuria was not unexpected in women of this age group complaining of urinary symptoms.

The serum oestradiol levels in the women given an active implant increased within one month of implantation and, although gradually decreasing, remained elevated throughout the study period. The levels obtained were sufficient to have an impact on the endometrium and it is therefore likely that they were also high enough to affect the female lower urinary tract. A number of different outcome measures were used to assess the efficacy of the treatment as there is at present no single "Gold Standard" tool which adequately highlights success or failure of a particular therapy.

One of the problems in comparing studies of different types of treatment for urinary symptoms or incontinence is that different definitions of cure are used. For example, some authors only accept that a treatment has been successful when there is complete absence of a specific symptom while others may allow a greater than 50% improvement in its severity. To allow comparison with the previous largest study of oestrogen for the urge syndrome (Cardozo et al 1993b) the same strict definition of cure was used for analysis of the data from the urinary symptoms questionnaire. Cure was therefore defined as the complete absence of a specific urinary symptom which was present on entry to the study.

The only significant change found using the urinary symptoms questionnaire was that 44% of women complaining of urge incontinence at the start of the study were cured of this problem. However, this was not statistically better than the control group because in common with other studies the placebo response rate was 30%. The cure rates for urgency and stress incontinence were disappointingly low and again not statistically better than placebo. The 80% cure rate of dysuria in the women given oestradiol needs to be interpreted with caution at this stage as there were only eight women complaining of this symptom at the start of the study. Assessment of quality of life using the King's Health questionnaire also indicated that the treatment was largely

unsuccessful with no significant changes occurring in any of the domains measured. Overall, the subjective results are very similar to those reported by Cardozo and colleagues (1993b) and certainly do not suggest that oestradiol implants are more efficacious for the treatment of the "urge syndrome" than oral oestriol.

The largest changes were seen in the visual analogue scores, which provided an assessment of the severity of the urinary symptoms. Improvements tended to start soon after implantation and continue to the end of the study. However, again these changes were found in both the oestradiol and placebo groups for reasons which are discussed below. It can therefore be concluded that these preliminary results suggest that oestradiol does not produce an improvement in the *symptoms* of the "urge syndrome" greater than that found with placebo.

Objective measurements of the changes in voiding pattern and bladder function were made using frequency volume charts and urodynamic studies. While there was a small reduction in the number of voids /24 hours in the women given oestradiol there were no statistical differences between the groups at the end of the study. In common with previous work (Fantl et al 1988) oestradiol was shown to increase the sensory threshold of the bladder and slightly increase the bladder capacity. There were no changes in the parameters of the women randomised to placebo. This may be because there were more women with underlying abnormal detrusor activity (75%) in this group compared to those patients treated with oestradiol (25%). It may be possible to say at the end of the study if the only women to respond to treatment are those without abnormal detrusor activity on cystometry. However, the numbers in each diagnostic group (abnormal detrusor activity or no abnormal detrusor activity) at this stage are too small for meaningful analysis. There was a wide range in the urethral pressure profilometry measurements. As discussed in **Chapter four** this finding has been

reported by several authors and severely limits the value of this test both in a clinical and research setting. Probably for this reason there were no significant changes in any of the parameters of the urethral pressure profile three months after implantation.

12.8.3 Safety and tolerability of 25mg oestradiol implants

The secondary objective of this study was to assess the safety and tolerability of 25mg oestradiol implants as a treatment for the "urge syndrome." Administration of oestrogen using subcutaneous implants has been in clinical practice for many years and the implantation procedure itself was found to be widely acceptable to the women. However, the onset of vaginal bleeding was a major cause of dissatisfaction and significantly reduced the acceptability of the treatment to the women affected. The high incidence of bleeding was greater than that reported with oral preparations (Sturdee et al 1978, Jackson et al 1999) and was largely unexpected at the start of the study. It may be that the endometrium was more susceptible to the continuously elevated levels of oestrogen achieved when an implant is used compared to the fluctuations in serum oestradiol concentration found with other forms of HRT administration.

Although the vaginal bleeding tended to be light and largely controlled by the addition of progestogens it was persistent in nature and unwanted by the women, several of whom had stopped their periods many years previously. The additional use of a progestogen may also have had an adverse effect on the urinary symptoms of some of the women and altered their response to the treatment given. The magnitude of this effect is difficult to assess and therefore all the subjects continued with their assessments and the results were analysed on an intention to treat basis. It is clearly of great concern that one patient had vaginal bleeding to the extent that she required a curettage and subsequent hysterectomy. Significant endometrial pathology had been

excluded by ultrasound on the baseline assessment and there was no evidence of hyperplasia or malignancy on either histological examination following her surgical procedures. The finding of an acute inflammatory infiltrate suggests that the patient developed a severe endometritis which may in part have accounted for her symptoms. However, the endometrium is clearly very sensitive to the effects of even low doses of oestrogen administered by implant and this severely impairs to possible use of this treatment in women with the "urge syndrome" who have not undergone a hysterectomy.

12.8.4 Do 25mg oestradiol implants have a potential role in the treatment of the "urge syndrome?"

These preliminary data suggest that when given alone 25mg oestradiol implants do not have a role in the treatment of the symptoms of the "urge syndrome." This is for two main reasons.

Firstly, even using a number of different outcome measures it was not possible to show any significant benefits of the active treatment, mainly because of the large placebo effect. This is a feature in common with other randomised studies of medical interventions, including previous controlled trials of oestrogen for the "urge syndrome" (**Table 6.3.**). The word placebo ("I shall please") was first used in the 14th century (Shapiro 1964). Until the first half of the 20th century the use of placebos was widespread in medicine (Craen et al 1999). However, it was not until 1938 that the word placebo was first applied in reference to the treatment given to concurrent controls in a trial (Diehl et al 1938). While using placebos in research, clinicians began to realise the therapeutic value of administering inert preparations. In a review of 15 placebo controlled trials it was concluded that, on average, the magnitude of the placebo effect was 32.5% (Beecher 1955). The placebo effect largely explains the fact that

while observational studies of oestrogen for urinary symptoms often show a subjective benefit, randomised trials have shown that when oestrogen is given alone there is virtually no additional improvement.

The large placebo response found in this study may have occurred for a number of reasons. As a consequence of completing the frequency volume charts the women may have become more aware of their fluid intake and voiding pattern. In addition, although they were not instructed to do so they may in fact have been effectively undergoing a form of bladder retraining. Also, as with the treatment of a number of chronic conditions, the fact that I was seeing them personally on a regular basis, providing support and taking great interest in their progress may itself have produced an improvement. Regular urine culture and early treatment of urinary tract infection is also likely to have led to a symptomatic improvement in both treatment groups.

Secondly, the use of 25mg oestradiol implants for this condition is also severely limited by the side effect of vaginal bleeding in patients who have not undergone a hysterectomy. At this stage of the study it is difficult to assess if those women who have had a hysterectomy, or do not have any vaginal bleeding, feel that their response to treatment is better than those who have had this side effect. However, it should be concluded that if oestrogen therapy is going to be used at all in this way for the "urge syndrome" then it should probably be restricted to women without a uterus. Treatment may also have to be limited to those women without underlying abnormal detrusor activity on urodynamics. The problem is that to further restrict this treatment would mean that very few women referred to a hospital department would be likely to benefit. Perhaps the best way forward would be to study the combined effect of oestrogen therapy with other treatments. This is discussed further in **Chapter 13.**

SECTION THREE

CHAPTER 13

FINAL CONCLUSIONS AND FUTURE RESEARCH

13.1. Impact of sex steroids on the aetiology of urinary symptoms

Detailed evidence has been presented which demonstrates that sex hormones have an important role in female lower urinary tract function throughout adult life. These effects probably occur through a number of mechanisms including a central effect on the brain and a local action on the bladder, urethra and pelvic floor. As the population of postmenopausal women in the community continues to grow an understanding of the effects of sex hormones on the bladder, and the possible benefits of oestrogen replacement therapy on urinary dysfunction, has become increasingly important. The studies reported in this thesis add significantly to our knowledge in this area.

Hormonal fluctuations during the menstrual cycle may lead to both symptomatic and functional changes. It is now clear that as many as 40% of pre-menopausal women recognise a cyclical pattern to their bladder problems with the time just before menstruation appearing to be the most bothersome. The prevalence of abnormal detrusor activity detected on videocystourethrography also increases during the luteal phase of the menstrual cycle even in women who do not feel that their symptoms have a cyclical pattern. These observations are likely to be secondary to changes in the circulating level of progesterone following ovulation. Timing of urodynamic investigation within the menstrual cycle may, therefore, be important. However, it is at present unclear if symptomatic women who have a normal study during the follicular phase of the menstrual cycle should have their study repeated during the luteal phase. In addition, it is uncertain if suppression of the normal menstrual cycle may improve urinary symptoms in some women and also alter the detection of abnormal detrusor activity. Further research is needed to answer these questions.

It is known that some incontinent women on HRT have an increase in urinary leakage during the progestogenic phase of their treatment (Benness et al 1991). At

present it is unknown if there is also an increase in the prevalence of abnormal detrusor activity at this time. Performing urodynamic studies at different times within a HRT cyclical (oestrogen only or oestrogen in combination with progestogen) may give further insight into the effect of progestogens on the female lower urinary tract. Indeed, it is possible that similar changes may occur to those found during the normal menstrual cycle. Further evaluation of the urinary symptoms of women with regular menstrual cycles or those on cyclical HRT could also be made using bladder diaries. Women could be asked to record the severity of different urinary symptoms daily, perhaps over a period of three months. It may then be possible to estimate the degree by which individual urinary symptoms change in relation to fluctuations in sex steroid levels, although other non-hormonal variables such as work and leisure activities would need to be taken into account.

The mean age of women referred for urodynamic investigation coincides with the age of the natural menopause. However, relatively few patients feel that this is the main cause of their urinary problems. Although a number of epidemiological reports have implicated the menopause in the aetiology of urinary symptoms it has been difficult to separate this observation from the concurrent effects of ageing. It has now been shown that young women with eating disorders and associated oestrogen deficiency also have a high prevalence of urinary symptoms which have a significant impact on their quality of life. Unfortunately, it is difficult to be certain of the underlying changes that may account for these findings, as the women are usually very reluctant to undergo urodynamic investigation. Further work is necessary to establish if symptoms improve when oestrogen levels return to normal as weight is gained. However, as anorexia nervosa tends to run a chronic course lasting for many years, prospective studies may prove difficult to perform.

The recent finding that there is more than one type of oestrogen receptor has provided an exciting area for further research. It would be interesting to determine the distribution of ERα and ERβ receptor subtypes in the lower urinary tract in more detail. It is possible that different rates of receptor expression may be found in premenopausal and postmenopausal women. In addition, the distribution and expression of different oestrogen receptor subtypes may vary between women with urogenital symptoms (including incontinence, the "urge syndrome" and prolapse) and normal controls.

The menopause and oestrogen deficiency are thought to be important factors in the aetiology of recurrent urinary tract infection but their impact on this condition may have previously been overstated. Although oestrogen may change vaginal flora, the results of randomised studies of oestrogen for prophylaxis against recurrent urinary tract infections have given conflicting and largely disappointing results. Analysis in this thesis has shown that the proportion of infected urine samples increases with age but no significant changes occur at the time of or following the menopause. Therefore, the effects of ageing in community dwelling women appear to be more important than the changes in the female lower urinary tract induced by falling levels of oestrogen.

13.2 Role of oestrogen replacement therapy in the treatment of the "urge syndrome"

Symptoms of postmenopausal urogenital atrophy have been shown to respond to hormone replacement therapy, particularly when oestradiol is given by the vaginal route (Smith et al 1993). It is therefore surprising, given that the menopause has also been associated with the development of urinary symptoms, that oestrogen replacement therapy has been shown to be so ineffective in the treatment of a number of different lower urinary tract complaints. While improvements have been noted in observational

studies, none of the randomised controlled trials reported so far have shown an advantage over placebo. Although the study reported in this thesis is yet to be completed, at this stage it is difficult to justify the continued use of oestrogen alone to treat the "urge syndrome" in clinical practice. Even using oestradiol implants in a dose high enough to cause significant problems with the endometrium, no therapeutic benefits above those of placebo have been observed despite using multiple assessments. It is unlikely that further research using oestrogen alone, either in a higher dosage or by using an alternative route of administration, will lead to different conclusions.

Oestrogen has been shown to be more effective when used in combination with alpha-adrenergic agents for the treatment of stress incontinence. It would be interesting to determine if other conservative treatments for stress incontinence (such as pelvic floor exercises) or surgical approaches (such as colposuspension or periurethral injections) are more effective when women are also given oestrogen replacement. Oestrogen may also have a role in the treatment of urgency and urge incontinence when used in combination with other therapies. As oestrogen has been shown to have a direct action on the bladder it is possible that it may be more efficacious in treating the "urge syndrome" when given in combination with other medications such as anticholinergics. This may form the basis of further work. For example, it would be possible to determine if agents such as oxybutynin or tolterodine are more effective in women who are taking hormone replacement therapy compared to those who are oestrogen deficient. Recruiting women into such a study would almost certainly be possible (and probably easier than for a trial of oestrogen alone) because a treatment of proven efficacy would also be offered. The community or general practice may be an ideal setting for such a study so as to include patients with a wider range of symptom severity than that which may be found in hospital practice.

Apart from its lack of efficacy, one of the biggest problems with using oestrogen therapy to treat urinary symptoms is the unwanted effect on the endometrium and associated vaginal bleeding. To overcome this problem several approaches could be considered in the future.

Firstly, it may be possible to prevent vaginal bleeding in some women treated with oestrogen by inserting a progestogen directly into the uterus. One example of this is the Mirena intra-uterine system which releases levonorgestrel directly into the uterine cavity. The adverse effect of progesterone on the bladder may therefore be minimised (as relatively little is absorbed), and hopefully in most cases vaginal bleeding will be avoided. However, it is unlikely that many women, and in particular elderly patients who are most likely to complain of the "urge syndrome", would be willing to either try or take part in a study of this treatment when potentially more effective alternatives are available.

Secondly, as dislike of vaginal bleeding is a major factor leading to non-compliance of sequential combined therapies, alternative types of HRT may be studied. With continuous combined HRT a progestogen is added to oestrogen to provide a continuous dose of both hormones. With this treatment progestogen counteracts the proliferative effect of oestrogen on the endometrium, so there is little or no shedding. The endometrium is therefore maintained in an atrophic state while the systemic benefits of oestrogen are maintained. Almost all women on continuous combined HRT stop bleeding within a year of starting therapy and a large proportion of women become amenorrhoeic immediately or after a few months of treatment (Ulrich et al 1997). In a recent study the effects of continuous combined HRT on the bladder have been reported for the first time. In a non-randomised, dose finding observational study of 102 women Kok and colleagues (1999) reported an improvement in urinary frequency, nocturia and

incontinence after 6 months of treatment. However, lack of baseline urodynamic studies, objective outcome measures and a control group indicate that further work is required to demonstrate if this effect is greater than that of a placebo.

The third option, and another area for potential research, is the use of selective oestrogen receptor modulators (SERMs). Endogenous or therapeutically administered oestrogens mediate their biological effects mainly through oestrogen receptors which are found in a number of different tissues including breast, bone, liver and brain as well as the urogenital tract. SERMs bind to oestrogen receptors and show a mixed pattern of agonist and antagonist activity which is specific for a particular tissue. Increased interest in this area has coincided with the release of raloxifene, which is licensed for the prevention of non-vertebral fractures in postmenopausal women at increased risk of osteoporosis. This SERM has oestrogen like actions in bone and liver and blocks the effects of oestrogen on the breast. Raloxifene also appears to have little or no agonist activity on the endometrium. In a two-year placebo controlled study involving 601 postmenopausal women, raloxifene did not increase endometrial thickness (assessed by transvaginal ultrasonography) or the frequency of vaginal bleeding (3% with raloxifene, 2.2% with placebo) (Delmas et al 1997). There are at present no published data on the effects of raloxifene on the lower urinary tract and it would be very interesting to determine the action of this and other SERMs on this area. In the longer term, it is exciting to speculate that it may be possible to develop a SERM which acts principally on the female bladder and urethra, with minimal unwanted effects on other tissues. The therapeutic benefit for women with urogenital disorders may be considerable, and significantly greater than the disappointing effect of oestradiol implants on the "urge syndrome" found in this thesis.

REFERENCES

Abrams P, Feneley R, Torrens M. Urodynamic investigations. In :Urodynamics. Berlin: Springer-Verlag, 1983: 35-39.

Abrams P, Blaivas JG, Stanton SL, Anderson JT. The standardisation of terminology of lower urinary tract dysfunction. Br J Obstet Gynaecol 1990; **97**: 1-16.

Adatto K, Doebele KG, Galland L, Granowetter L. Behavioural factors and urinary tract infection. JAMA 1979; **241**: 2525-6.

Ahlstrom K, Sandahl B, Sjorberg B, Ulmsten U, Stormby N, Lindskog M. Effect of combined treatment with phenylpropanolamine and estriol, compared with estriol alone, in postmenopausal women with stress incontinence. Gynecol Obstet Invest 1990; **30**: 37-43.

Akhtar AJ, Andrews GR, Caird FL. Urinary tract infection in the elderly. Age and Ageing 1972; **1**: 48-54.

Alcoff JM, Campbell D, Tribble D, Oldfield B, Cruess O. Double blind, placebo controlled crossover trial of Propanolol as treatment for vasomotor symptoms. Clin Ther 1981; **3**: 356-64.

Allen RE, Warrell DW. The role of pregnancy and childbirth in the partial denervation of the pelvic floor. Neurourol Urodyn 1992; **6**: 183-4.

Altman DG. Types of data. In: Practical statistics for medical research. London: Chapman & Hall, 1991: 10-18.

Andersson KE. Pharmacology of the lower urinary tract smooth muscles and penile erectile tissues. Pharmacol Rev 1993; **45**: 253-308.

Andersson KE. The overactive bladder: pharmacological basis of drug treatment. Urology 1997; **50**: 74-84.

Appell RA. Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. Urology 1997; **50**: 90-6.

Archer DF, McIntyre-Seltman K, Wilborn WW, et al. Endometrial morphology in asymptomatic postmenopausal women. Am J Obstet Gynecol 1991; **165**: 317-22.

Bachrach LK, Katzman DK, Litt I, Guido D, Marcus R. Recovery from osteopenia in adolescent girls with anorexia nervosa. J Clin Endocrin Metab 1991; **72**: 602-6.

Baldassarre JS, Kaye D. Special problems of urinary tract infections in the elderly. Medical Clinics of North America 1991; **75**: 375-90.

Balen AH, Jacobs HS. Investigating infertility. In: Infertility in practice. Edinburgh: Churchill Livingstone, 1997: 49-114.

Barlow DH, Brockie JA, Rees CMP. Study of general practice consultations and menopausal problems. BMJ 1991; **302**: 274-6.

Barlow DH, Cardozo LD, Francis RM, et al. Urogenital ageing and its effect on sexual health in older British women. Br J Obstet Gynaecol 1997; **104**: 87-91.

Barnick C. Frequency / Volume charts. In: Cardozo L, editor. Urogynaecology. London: Churchill Livingstone, 1997: 101-107.

Bates CP, Whiteside CG, Turner-Warwick RT. Synchronous cine-pressure-flow cystourethrography with special reference to stress and urge incontinence. Br J Urol 1970; **42**: 714-23.

Bates P, Bradley WE, Glen E. Standardisation of terminology of lower urinary tract function. J Urol 1979; **121**: 551-4.

Bates GW, Bates SR, Whitworth NS. Reproductive failure in women who practice birth control. Fertil Steril 1982; **37**: 373-8.

Batool T, Reginald PW, Hughes JH. Outpatient Pipelle endometrial biopsy in the investigation of postmenopausal bleeding. Br J Obstet Gynaecol 1994; **101**: 545-6.

Batra SC, Iosif CS. Progesterone receptors in the female lower urinary tract. J Urol 1987; **138**: 1301-4.

Batra S, Anderson KE. Oestrogen-induced changes in muscarinic receptor density and contractile responses in the female rat urinary bladder. Acta Physiol Scand 1989; **137**: 135-41.

Beecher HK. The powerful placebo. *JAMA 1955; **159**: 1602-6.*

Beisland HO, Fossberg E, Moer A, et al. Urethral insufficiency in postmenopausal females: treatment with phenylpropanolamine and estriol separately and in combination. Urol Int 1984; **39**: 211-6.

Benness C, Gangar K, Cardozo LD, Cutner A. Do progestogens exacerbate urinary incontinence in women on HRT? Neurourol Urodyn 1991; **10**: 316-8.

Benness C, Wise BG, Cutner A, Cardozo LD. Does low dose vaginal Estradiol improve frequency and urgency in postmenopausal women? Int Urogynecol J 1992; **3(2)**: 281.

Benness C. Cystometry. In: Cardozo L, editor. Urogynaecology. London: Churchill Livingstone,1997: 117-133.

Berghmans LC, Hendricks HJ, Bo K, Hay-Smith EJ, de Bie RA, van Waalwijk van Doorn ES. Conservative treatment of stress incontinence in women. A systematic review of randomised clinical trials. Br J Urol 1998; **82**: 181-91.

Bergman A, Karram MM, Bhatia NN. Changes in urethral cytology following estrogen administration. Gynecol Obstet Invest 1990; **29**: 211-3.

Berkow SG. The corpus spongiosum of the urethra: its possible role in urinary control and stress incontinence in women. Am J Obstet Gynecol 1953; **65**: 346-51.

Bernstein IT. The pelvic floor muscles: Muscle thickness in healthy and urinary incontinent women measured by perineal ultrasonography with reference to the effect of pelvic floor training. Estrogen receptor studies. Neurourol Urodyn 1997; **16**: 237-75.

Best NR, Rees MP, Barlow DH, et al. Effect of estradiol implant on noradrenergic function and mood in menopausal subjects. Psychoneuroendocrinology 1992; **17**: 87-93.

Bhatia NN, Bergman A, Karram MM, et al. Effects of oestrogen on urethral function in women with urinary incontinence. Am J Obstet Gynecol 1989; **160**: 176-81.

Biller BM. Mechanism of osteoporosis in adult and adolescent women with anorexia nervosa. J Clin Endocrin Metab 1989; **68**: 548-54.

Billewicz W, Fellowes H, Thompson A. Pubertal changes in boys and girls in Newcastle upon Tyne. Ann Hum Biol 1981; **8**: 211-9.

Black NA, Downs SH. The effectiveness of surgery for stress incontinence in women: a systematic review. Br J Urol 1996; **78**: 497-510.

Blakeman PJ, Hilton P, Bulmer JN. Mapping oestrogen and progesterone receptors throughout the female lower urinary tract. Neurourol Urodyn 1996a; **15**: 324-5.

Blakeman PJ, Hilton P, Bulmer JN. Oestrogen status and cell cycle activity in the female lower urinary tract. Neurourol Urodyn 1996b; **15**: 325-6.

Blakeman PJ, Hilton P, Bulmer JN. Androgen receptors in the female lower urinary tract. Int Urogynecol J 1997; **8**: S54

Blok BFM, Holstege G. Androgen receptor immunoreactive neurons in the hypothalamic preoptic area project to the pontine micturition centre in the male cat. Neurourol Urodyn 1998; **17(4)**: 404-5.

Bo K, Larsen S, Oseid S, Kvarstein B, Hagen RH. Knowledge about and ability to correct pelvic floor muscle exercises in women with urinary stress incontinence. Neurourol Urodyn 1988; 7: 261-2.

Bo K, Hagen RH, Kvarstein B, Jorgensen J, Larsen S. Pelvic floor muscle exercise for the treatment of female stress urinary incontinence. III: Effects of two different degrees of pelvic floor muscle exercise. Neurourol Urodyn 1990; 9: 489-502.

Bo K. Pelvic floor muscle exercise for the treatment of stress urinary incontinence: An exercise physiology perspective. Int Urogynecol J 1995a; 6: 282-91.

Bo K. Vaginal weighted cones. Theoretical framework, effect on pelvic floor muscles strength and female stress urinary incontinence. Acta Obstet Gynecol Scand 1995b; 74: 87-92.

Bo K, Talseth T, Holme I. Single blind, randomised controlled trial of pelvic floor exercises, electrical stimulation, vaginal cones and no treatment in management of genuine stress incontinence in women. BMJ 1999; 318: 487-93.

Bonne OB, Bloch M, Berry EM. Adaptation to severe hypokalaemia: a plea for conservative management. Int J Eating Disorders 1993; 13(1): 125-8.

Boos K, Hextall A, Anders K, Cardozo L. Fastidious organisms and recurrent urinary tract infections: a clinical and bacterial review of 110 cases. Br J Urol 1997; 79(4): 38-9.

Boos K, Hextall A, Cardozo L, Toozs-Hobson P, Anders K, Treasure JL. Lower urinary tract symptoms and their impact on women with anorexia nervosa. Br J Obstet Gynaecol 1999; 106(5): 501-4.

Boscia JA, Kobasa WD, Knight RA, et al. Epidemiology of bacteriuria in an elderly ambulatory population. Am J Medicine 1986; 80: 208-14.

Bradbury RB, White DC. Oestrogens and related substances in plants. Vit Horm 1954; 12: 207-33.

Brading AF. A myogenic basis for the overactive bladder. Urology 1997; **50**: 57-67.

Brandberg A, Mellstrom D, Samsioe G. Low dose oral oestriol treatment in elderly women with urogenital infections. Acta Obstet Gynecol Scand 1987; **140**: 33-8.

Bro-Rasmussen F, Halborg Sorensen A. The structure and function of the urinary bladder. Urol Int 1965; **19**: 280-95.

Brocklehurst JC, Dillane JB, Griffiths L, et al. The prevalence and symptomatology of urinary tract infection in aged population. Gerontology Clinics 1968; **10**: 242-53.

Brocklehurst JC. Ageing of the human bladder. Geriatrics 1972; **27**: 154.

Brocklehurst JC, Bee P, Jones D, Pamer M. Bacturia in geriatric hospital patients: its correlates and management. Age and Ageing 1977; **6**: 240-5.

Brocklehurst JC. Urinary incontinence in the community-analysis of a MORI poll. BMJ 1993; **306**: 832-4.

Buckley RM, McGuckin M, MacGregor RR. Urine bacterial counts after sexual intercourse. New Eng J Med 1978; **298(6)**: 321-4.

Bump RC, Copeland WE, Hurt WG. Dynamic urethral pressure / profilometry pressure transmission ratio determination in stress-incontinent and stress-continent women. Am J Obstet Gynecol 1988; **159**: 749-55.

Bungay G, Vessey MP, McPherson CK. Study of symptoms in middle life with special reference to the menopause. BMJ 1980; **281**: 181-3.

Burgio KL, Robinson JC, Engel BT. The role of biofeedback in Kegel exercise training for stress urinary incontinence. Am J Obstet Gynecol 1986; **154**: 58-63.

Burgio KL, Matthews KA, Engel B. Prevalence, incidence and correlates of urinary incontinence in healthy, middle aged women. J Urol 1991; **146**: 1255-9.

Burton G, Cardozo LD, Abdalla H, Kirkland A, Studd JW. The hormonal effects on the lower urinary tract in 282 women with premature ovarian failure. Neurourol Urodyn 1992; **10**: 318-9.

Cardozo L, Stanton SL. Detrusor instability following surgery for genuine stress incontinence. Br J Obstet Gynaecol 1979; **51**: 204-7.

Cardozo L, Stanton SL. Genuine stress incontinence and detrusor instability: a review of 200 cases. Br J Obstet Gynaecol 1980; **87**: 184-90.

Cardozo LD, Tapp A, Versi E. The lower urinary tract in peri- and postmenopausal women. In: Samsioe G, Bonne Erickson P, editors. The Urogenital Oestrogen Deficiency Syndrome. Bagsverd, Denmark: Novo Industri AS, 1987: 10-17.

Cardozo L. Role of estrogens in the treatment of female urinary incontinence. J Am Geriatr Soc 1990; **38**: 326-8.

Cardozo L, Cutner A, Wise BG. Investigation of lower urinary tract dysfunction. In: Basic urogynaecology. Oxford: Oxford University Press, 1993a: 42-70.

Cardozo LD, Rekers H, Tapp A, et al. Oestriol in the treatment of postmenopausal urgency: a multicentre study. Maturitas 1993b; **18**: 47-53.

Cardozo LD, Benness C, Abbott D. Low dose oestrogen prophylaxis for recurrent urinary tract infections in elderly women. Br J Obstet Gynaecol 1998; **105**: 403-7.

Cardozo L, Lose G, McLish D, Versi E, De Koning Cans H. A systematic review of estrogens for recurrent urinary tract infections. Int Urogynecol J 1999; **10 (Suppl 1)**: S32.

Carlile A, Davies J, Faragher E, et al. The epithelium of the female urethra. J Urol 1987; **138**: 775.

Cattell WR. Urinary tract infection: definitions and classification. In: Infections of the kidney and urinary tract. Oxford: Oxford University Press, 1996: 1-7.

Caulfield MP, Birdsall NJM. Classification of muscarinic acetylcholine receptors. Pharmacol Rev 1998; **50**: 279-90.

Chakravarti S. Hormone profiles after the menopause. BMJ 1976; **2**: 784-7.

Chaliha C, Kalia V, Stanton SL, Sultan AH, Monga AK. What does pregnancy and delivery do to bladder function? A urodynamic viewpoint. Neurourol Urodyn 1998; **17(4)**: 415-6.

Chen GD, Oliver RH, Leung BS, Lin LY, Yeh J. Estrogen receptor alpha and beta expression in the vaginal walls and uterosacral ligaments of premenopausal and postmenopausal women. Fertil Steril 1999; **71(6)**: 1099-102.

Choudhury SL, Brocklehurst JC. Urinary infections in the elderly. In: Brumfitt W, Hamilton-Miller JMT, Bailey RR, editors. Urinary tract infections. Cambridge: University Press, 1998: 229-243.

Christie D, Bryant-Waugh R, Lask B. Neurobiological aspects of early onset eating disorders. In: Hoek HW, Treasure JL, Katzman MA, editors. Neurobiology in the treatment of eating disorders. Chichester: John Wiley and Sons Ltd,1998: 291-309.

Clark JH, Hardin JW, McCormack SA. Estrogen receptor binding and growth of the reproductive tract. Paediatrics 1978; **62**: 33-7.

Clayden JR, Bell JW, Pollard P. Menopausal flushing: double blind trial of a non-hormonal preparation. BMJ 1974; **1**: 409-12.

Collas DM, Malone Lee J. Age-associated changes in detrusor sensory function in women with lower urinary tract symptoms. Int Urogynecol J 1996; **7**: 24-9.

Cornier C. The Pipelle: A disposable device for endometrial biopsy. Am J Obstet Gynecol 1984; **148**: 109-10.

Craen AJM, Kaptchuk TJ, Tijssen JGP, Kleijnen J. Placebos and placebo effects in medicine: historical review. Journal of the Royal Society of Medicine 1999; **92**: 511-5.

Cutner A, Carey A, Cardozo LD. Lower urinary tract symptoms in early pregnancy. J Obstet Gynaecol 1992; **12**: 75-8.

Cutner A. The lower urinary tract in pregnancy. MD Thesis: University of London, 1993.

Cutner A, Burton G, Cardozo LD, Wise BG, Abbot D, Studd JW. Does progesterone cause an irritable bladder? Int Urogynecol J 1993; **4(259)**: 261.

Cutner A. Uroflowmetry. In: Cardozo L, editor. Urogynaecology. London: Churchill Livingstone, 1997: 109-116.

De Groat WC, Nadelhaft I, Milne RJ, Booth AM, Morgan C, Thor K. Organization of the sacral parasympathetic reflex pathways to the urinary bladder and large intestine. J Auton.Nerv.Syst 1981; **3**: 135-60.

De Groat WC, Booth AM, Yoshimura N. Neurophysiology of micturition and its modification in animal models of human disease. In: Maggi CA, editor. Nervous control of the urogenital system. London: Harwood academic publishers,1993: 227-290.

De Groat WC. A neurological basis for the overactive bladder. Urology 1997; **50**: 36-52.

De Groat WC, Downie JW, Levin RM, et al. Basic neurophysiology and neuropharmacology. In: Abrams P, Khoury S, Wein A, editors. Incontinence (1st International Consultation on Incontinence of the World Health Organization). Plymouth: Health Publications Limited, 1999: 105-154.

DeLancey JOL. Correlative study of paraurethral anatomy. Obstet Gynecol 1986; **68**: 91.

DeLancey JOL. Anatomy and mechanics of structures around the vesical neck: how vesical position may affect its closure. Neurourol Urodyn 1988; **7(3)**: 161-2.

DeLancey JOL. Anatomic aspects of vaginal eversion after hysterectomy. Am J Obstet Gynecol 1992; **166**: 1717-28.

Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. New Eng J Med 1997; **337**: 1641-7.

Diehl HS, Baker AB, Cowan DW. Cold vaccines. An evaluation based on a controlled trial. JAMA 1938; **111**: 1168-73.

Diep N, Constantinou CE. Age dependent response to exogenous estrogen on micturition, contractility and cholinergic receptors of the rat bladder. Life Sciences 1999; **64**: 279-89.

Diokno AC, Brock BM, Brown MB, Herzog AR. Prevalence of urinary incontinence and other urological symptoms in the non-institutionalised elderly. J Urol 1986; **136**: 1022-5.

Ditkoff EC, Crary WG, Cristo M. Estrogen improves psychological function in asymptomatic postmenopausal women. Obstet Gynecol 1991; **78**: 991-5.

Dontas AS, Kasviki-Charvati P, Papanayiotou PC. Bacturia and survival in old age. New Eng J Med 1981; **304**: 939-43.

Droes JTPM. Observations on the musculature of the urinary bladder and urethra in the human fetus. Br J Urol 1974; **46**: 179-85.

Dunn M, Smith JC, Ardran GM. Prolonged bladder distension as a treatment of urgency and urge incontinence of urine. Br J Urol 1974; **46**: 645-52.

Eglen RM, Hegde SS, Watson N. Muscarinic receptor subtypes and smooth muscle function. Pharmacol Rev 1996; **48**: 531-65.

Ek A, Anderson KE, Gullberg B, et al. Effects of oestradiol and combined norephedrine and oestradiol treatment on female stress incontinence. Zentralbl Gynaekol 1980; **102**: 839

Ekelund P, Rundgren A. Urinary incontinence in the elderly with implications for hospital care consumption and social disability. Arch Geront Geriatr 1987; **6**: 11-8.

Ekelund P, Grimby A, Milsom I. Urinary incontinence: social and financial costs high. BMJ 1993; **306**: 1344

Ekstrom J, Iosif CS, Malmberg L. Effects of long-term treatment with estrogen and progesterone on in vitro muscle responses of the female rabbit urinary bladder and urethra to autonomic drugs and nerve stimulation. J Urol 1993; **150**: 1284-8.

Elliott RA, Castleden CM, Miodrag A, Kirwan P. The direct effects of diethylstilboestrol and nifedipine on the contractile responses of isolated human and rat detrusor muscles. Eur J Clin Pharmacol 1992a; **43**: 149-55.

Elliott RA, Castleden CM, Miodrag A. The effect of *in vivo oestrogen* pretreatment on the contractile response of rat isolated detrusor muscle. Br J Pharmacol 1992b; **107**: 766-70.

Elliott RA, Castleden CM. Effect of progestogens and oestrogens on the contractile response of rat detrusor muscle to electrical field stimulation. Clinical Science 1994; **87**: 337-42.

Enmark E, Gustafsson JA. Oestrogen receptors-an overview. Journal of Internal Medicine 1999; **246**: 133-8.

Enzelsberger H, Kurz C, Schatten C, Huber J. The effectiveness of intravaginal estriol tablet administration in women with urge incontinence. Geburtshilfe-Frauenklinik 1991; **51**: 834-8.

Eriksen B. A randomized, open, parallel group-study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. Am J Obstet Gynecol 1999; **180**: 1072-9.

Ervine C, Komaroff AL, Pass TM. Behavioural factors and urinary incontinence. JAMA 1980; **243**: 330-1.

Evans DA. Bacteriuria in a population-based cohort of women. J Infect Dis 1978; **138**: 768-73.

Ewing R, Bultitude MI, Shuttleworth KED. Subtrigonal phenol injection for urge incontinence secondary to detrusor instability. Br J Urol 1982; **50**: 529-34.

Eykyn SJ. Urinary tract infections in the elderly. Br J Urol 1998; **82**: 79-84.

Fairburn CG, Norman PA, Welch SL, O'Connor ME, Doll HA, Peveler PC. A prospective study of outcome in bulimia nervosa and the long term effects of three psychological treatments. Arch Gen Psychiatry 1995; **52(4)**: 304-12.

Fall M, Lindstrom S, Mazieres L. A bladder-cooling reflex in the cat. J Physiol 1990; **427**: 281-300.

Fantl JA, Wyman JF, Anderson RL, et al. Postmenopausal urinary incontinence: comparison between non-estrogen and estrogen supplemented women. Obstet Gynecol 1988; **71**: 823-8.

Fantl JA, Cardozo LD, McClish DK, et al. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. Obstet Gynecol 1994; **83**: 12-8.

Fantl JA, Bump RC, Robinson D, et al. Efficacy of estrogen supplementation in the treatment of urinary incontinence. Obstet Gynecol 1996; **88**: 745-9.

Fiodart JM, Vervliet J, Buyaert P. Efficacy of sustained-release vaginal oestriol in alleviating urogenital and systemic complaints. Maturitas 1991; **13**: 99-107.

Fombonne E. Anorexia nervosa. No evidence of an increase. British Journal of Psychiatry 1995; **166**: 462-71.

Fothergill DJ, Brown VA. Histological sampling of the endometrium - a comparison between formal curettage and the Pipelle sampler. Br J Obstet Gynaecol 1992; **99**: 779-80.

Foxman B, Frerichs RR. Epidemiology of urinary tract infection 1. Diaphragm use and sexual intercourse. American Journal of Public Health 1985; **75**: 1308-13.

Fraser IS, Wang Y. New delivery systems for HRT. In: Studd JW, editor. Modern management of the menopause. Annual review 1998. Carnforth, Lancs: Parthenon, 1998: 101-110.

Frazer JE. The terminal part of the Wolffian duct. J Anat 1935; **69**: 455-68.

Freedman LR, Phair JP, Seki M, et al. The Epidemiology of urinary tract infections in Hiroshima. Yale Journal of Biology and Medicine 1965; **37**: 262-82.

Frewen WK. A reassessment of bladder training in detrusor dysfunction in the female. Br J Urol 1982; **54**: 372-3.

Frisch R, Revelle R. Heights and weights at menarche and a hypothesis of menarche. Arch Dis Childhood 1971; **46**: 695-701.

Ganger KF, Vyas S, Whitehead RW, et al. Pulsatility index in the internal carotid artery in relation to transdermal oestradiol and time since the menopause. Lancet 1991; **338**: 839-42.

Ganitkevich VY, Isenberg G. Depolarisation mediated intracellular calcium transients in isolated smooth muscle cells of guinea-pig urinary bladder. J Physiol 1995; **435**: 187-205.

Garner DM, Garfinkel PE. The Eating Attitudes Test: an index of symptoms of anorexia nervosa. Psychological Medicine 1979; **9**: 273-9.

Garner DM, Olmsted MP, Bohr Y, Garfinkel PE. The Eating Attitudes Test: Psychometric features and clinical correlates. Psychological Medicine 1982; **12**: 871-8.

Gjorup T, Hendriksen C, Lund E, et al. Is growing old a disease? A study of the attitudes of elderly people to physical symptoms. J Chron Dis 1987; **40**: 1095-8.

Goldchmit R, Katz Z, Blickstein I, Casp B, Dgni R. The accuracy of endometrial Pipelle sampler with and without sonographic measurements of endometrial thickness. Obstet Gynecol 1993; **82**: 727-30.

Gordon T, Castelli WP, Hjorteand MC, Kannal WO, Dauber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Obstet Gynecol 1977; **62**: 707-14.

Gorton E, Stanton SL. Women's attitudes to urodynamics: a questionnaire survey. Br J Obstet Gynaecol 1999; **106(8)**: 851-6.

Gosling J, Dixon JS. The structure and innervation of smooth muscle in the wall of the bladder neck and proximal urethra. Br J Urol 1975; **47**: 549-58.

Gosling J, Dixon JS, Critchley HOD, Thompson SA. A comparative study of the human external sphincter and periurethral levator ani muscles. Br J Urol 1981; **53**: 35-41.

Gosling J, Alm P, Bartsch G, et al. Gross anatomy of the lower urinary tract. In: Abrams P, Khoury S, Wein A, editors. Incontinence (1st International Consultation on Incontinence of the World Health Organization). Plymouth: Health Publications Limited, 1999: 21-56.

Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol 1995; **85**: 304-13.

Grimby A, Milsom I, Wiklund I, Ekelund P. The influence of incontinence on the QoL of elderly women. Age and Ageing 1993; **22**: 82-9.

Gross J, Rosen JC, Leitenberg H, Willmuth M. Validity of Eating Attitudes Test and the Eating Disorder Inventory in bulimia nervosa. J Consult Clin Psychol 1986; **54**: 875-6.

Gruneberg RN. Changes in urinary pathogens and their antibiotic sensitivities. Journal of Antimicrobial Chemotherapy 1994; **33**: 1-8.

Gull WW. Anorexia nervosa. Trans Clin Soc 1873; **7**: 22-8.

Gyllensten L. Contributions to the embryology of the urinary bladder. Acta Anat 1949; **7**: 305-44.

Haataja M, Paul R, Gronroos M, et al. Effect of prostaglandin inhibitor and estrogen on climacteric symptoms and serum free fatty acids. Maturitas 1984; **89**: 464-72.

Habler HJ, Janig W, Koltzenberg M. Activation of unmyelinated afferent fibres by mechanical stimuli and inflammation of the urinary bladder in the cat. J Physiol 1990; **425**: 545-62.

Henalla S, Hutchins C, Robinson P, MacVicar J. Non-operative methods in the treatment of female genuine stress incontinence of urine. J Obstet Gynaecol 1989; **92**: 22-5.

Henning C, Tornvall G. Bacterial contamination of urine, collected in fractions from different phases of micturition. Scandanavian Journal of Infectious Diseases 1975; **7**: 197-200.

Henry CJK. Variability in adult body size: uses in defining the limits of human survival. In: Ulijaszek SJ, Mascie-Taylor CGN, editors. Anthropometry: The Individual and the Population. London: Cambridge University Press, 1994: 117-129.

Herrington LJ, Weiss NS. Postmenopausal unopposed oestrogens. Characteristics of use in relation to the risk of endometrial carcinoma. Ann Epidemiol 1993; **3**: 308-18.

Herzog W, Detor HC, Schellberg D. Somatic findings at 12 year follow-up of 103 anorexia nervosa patients: Results of the Heidelberg-Mannheim follow-up. In: Herzog W, Deter HC, Vandereycken W, editors. The course of eating disorders. Berlin: Springer, 1992: 85-107.

Herzog W, Minne H, Deter HC, et al. Outcome of bone mineral density in anorexia nervosa patients 11.7 years after first admission. J Bone Min Res 1993; **8**: 597-603.

Hill K. The demography of the menopause. Maturitas 1996; **23**: 113-27.

Hilton P, Stanton SL. Urethral pressure measurements by microtransducer. The results in symptom-free and in those with genuine stress incontinence. Br J Obstet Gynaecol 1983a; **90**: 940-4.

Hilton P, Stanton SL. The use of intravaginal oestrogen cream in genuine stress incontinence. Br J Obstet Gynaecol 1983b; **90**: 940-4.

Hilton P, Tweddel AL, Mayne C. Oral and intravaginal estrogens alone and in combination with alpha adrenergic stimulation in genuine stress incontinence. Int Urogynecol J 1990; **12**: 80-6.

Hilton P. The mechanism of continence. In: Shaw R, Soutter P, Stanton SL, editors. Gynaecology. London: Churchill Livingstone, 1992: 581-595.

Hoek HW, Bartelds AIM, Bosweld JJF, et al. The impact of urbanization on the detection rates of eating disorders. Am Journal of Psychiatry 1995; **152**: 1272-8.

Holmes DM, Stone AR, Bary PR, Richards CJ, Stephenson TP. Bladder training 3 years on. Br J Urol 1983; **55**: 660-4.

Hooton TM, Scholes D, Hughes JP, Winter C, Roberts PL, et al. A prospective study of risk factors for symptomatic urinary tract infection in young women. New Eng J Med 1996; **335(7)**: 468-74.

Horan MA, Parker SG. Infections, aging and host response. In: Horan MA, Little RA, editors. Injury in the aging. Cambridge: Cambridge University Press, 1998: 126-146.

Hsu LKG. Outcome studies in patients with eating disorders. In: Mirin SM, Gossett JT, Grob MC, editors. Psychiatric Treatment Advances in Outcome Research. New York: American Psychiatric Press, 1991: 159-180.

Hsu LKG. Epidemiology of the eating disorders. The Psychiatric Clinics of North America 1996; **19**: 681-700.

Hu TW. Impact of urinary incontinence on health care costs. J Am Geriatr Soc 1990; **38**: 292-5.

Hunskaar S, Vinsnes A. The quality of life of women with urinary incontinence as measured by the sickness impact profile. J Am Geriatr Soc 1991; **39**: 378-82.

Incontinence. Causes, management and provision of services. London: The Royal College of Physicians, 1995.

Ingelman-Sundberg A. Partial bladder denervation for detrusor dyssynergia. Clinical Obstet Gynecol 1978; **21**: 797-805.

Ingelman-Sundberg A, Rosen J, Gustafsson SA. Cytosol oestrogen receptors in urogenital tissues in stress incontinent women. Acta Obstet Gynecol Scand 1981; **60**: 585-6.

Iosif CS, Batra S, Ek A. Estrogen receptors in the human female lower urinary tract. Am J Obstet Gynecol 1981; **141**: 817-20.

Iosif CS, Bekassy Z. Prevalence of genito-urinary symptoms in the late menopause. Acta Obstet Gynecol Scand 1984; **63**: 257-60.

Jackson S, Avery N, Shepherd A, Abrams P, Bailey A. The effect of oestradiol on vaginal collagen in postmenopausal women with stress urinary incontinence. Neurourol Urodyn 1996; **15(4)**: 327-8.

Jackson S, McDonnell C, James M, Shepherd A, Abrams P. Is postmenopausal urethral blood flow affected by hormone replacement therapy? A placebo controlled pilot study. Neurourol Urodyn 1997; **16(5)**: 352-3.

Jackson S, Vyas S. A double-blind, placebo controlled study of postmenopausal oestrogen replacement therapy and carotid artery pulsatility index. Br J Obstet Gynaecol 1998; **105(4)**: 408-12.

Jackson S, Shepherd A, Brookes S, Abrams P. The effect of oestrogen supplementation on post-menopausal urinary stress incontinence: a double-blind, placebo-controlled trial. Br J Obstet Gynaecol 1999; **106**: 711-8.

James M, Avery N, Jackson S, Bailey A, Abrams P. The pathophysiological changes of vaginal tissue in women with stress urinary incontinence: a controlled trial. Neurourol Urodyn 1999a; **18(4)**: 283-4.

James M, Avery N, Jackson S, Bailey A, Abrams P. The biochemical profile of vaginal tissue in women with genitourinary prolapse: a controlled trial. Neurourol Urodyn 1999b; **18(4)**: 284-5.

Jameson RM. Incontinence in women with neuropathic bladders. BMJ 1983; **287**: 627-8.

Janig W, Morrison JF. Functional properties of spinal visceral afferents supplying abdominal and pelvic organs, with special emphasis on visceral nociception. Prog Brain Res 1986; **67**: 87-114.

Jarvis GJ, Hall S, Stamp S, et al. An assessment of urodynamic investigation in incontinent women. Br J Obstet Gynaecol 1980; **87**: 184-90.

Jarvis GJ. A controlled trial of bladder drill and drug therapy in the management of detrusor instability. Br J Urol 1981; **53**: 565-6.

Jarvis GJ. Surgery for genuine stress incontinence. Br J Obstet Gynaecol 1994; **101**: 371-4.

Jeffcoate TNA, Francis WJA. Urgency incontinence in the female. Am J Obstet Gynecol 1966; **94**: 604-18.

Johnson M, Everitt B. Ovarian function. In: Essential reproduction. Edinburgh: Churchill Livingstone, 1984: 75-102.

Jolleys JV. Reported prevalence of urinary incontinence in a general practice. Br Med J 1988; **296**: 1300-2.

Judge TG. The use of quinestradiol in elderly incontinent women: A preliminary report. Gerontology Clinics 1969; **11**: 159-64.

Karram MM, Yeko TR, Sauer MV, et al. Urodynamic changes following hormone replacement therapy in women with premature ovarian failure. Obstet Gynecol 1989; **74**: 208-11.

Kass EH. Asymptomatic infections of the urinary tract. Transactions of the Association of American Physicians 1956; **69**: 56-63.

Kasviki-Charvati P, Drolette-Kefakis B, Papanayiotou PC. Turnover of bacturia in old age. Age and Ageing 1982; **11**: 169-74.

Kegel AH. Progressive resistance exercise in the functional restoration of the perineal muscles. Am J Obstet Gynecol 1948; **56**: 238-49.

Kelleher CJ, Cardozo L, Toozs-Hobson P. Quality of life and urinary incontinence. Current Opinion in Obstetrics and Gynaecology 1995; **7**: 404-8.

Kelleher CJ, Cardozo L, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. Br J Obstet Gynaecol 1997; **104(12)**: 1374-9.

Khullar V, Cardozo LD, Abbot D. Gax collagen in the treatment of urinary incontinence in elderly women: a two year follow-up. Br J Obstet Gynaecol 1997; **104**: 96-9.

King WJ, Greene GL. Monoclonal antibodies localized oestrogen receptor in nuclei of target cells. Nature 1984; **307**: 747.

Kinn AC, Lindskog M. Estrogens and phenylpropanolamine in combination for stress urinary incontinence in postmenopausal women. Urology 1988; **32**: 273-80.

Kirkengen AL, Anderson P, Gjersoe E, Johannessen GR, Johnsen N, Bodd E. Oestriol in the prophylactic treatment of recurrent urinary tract infections in postmenopausal women. Scan J Prim Health Care 1992; **10**: 139-42.

Kjaergaard B, Walter S, Knudsen A, Johansen B, Barlbeo H. Treatment with low dose vaginal estradiol in postmenopausal women. A double blind controlled trial. Ugeskr Laeger 1990; **152**: 658-9.

Klibansky A, Beverly M, Biller K, Schoenfeld D, Herzog DB, Saxe V. The effect of estrogen administration on trabecular bone loss in young women with anorexia nervosa. J Clin Endocrin Metab 1995; **80**: 898-904.

Kok ALM, Burger CW, van der Weijer PHM, Voetberg GA, Peters-Muller ERA, Kenemans P. Micturition complaints in postmenopausal women treated with continuously combined hormone replacement therapy: a prospective study. Maturitas 1999; **31**: 143-9.

Kolbl H, Strassegger H, Riis PA. Morphological and functional aspects of pelvic floor muscles in patients with pelvic relaxation and genuine stress incontinence. Obstet Gynecol 1989; **74**: 789-95.

Kondo A, Kato K, Saito M, et al. Prevalence of hand washing incontinence in females in comparison with stress and urge incontinence. Neurourol Urodyn 1990; **9**: 330-1.

Kondo S, Morita T, Tashima Y. Muscarinic cholinergic receptor subtypes in human detrusor studied by labelled and non-lablled pirenzepine. Urol Int 1995; **54**: 150-3.

Koziol JA. Epidemiology of interstitial cystitis. Urol Clin North Am 1994; **21**: 7-20.

Kuhl H. Pharmacokinetics of oestrogens and progestogens. Maturitas 1990; **12**: 171-97.

Kuiper G, Enmark E, Pelto-Huikko M, Gustafsson JA. Cloning of a novel oestrogen receptor in rat prostate and ovary. Proc Natl Acad Sci USA 1996; **93**: 5925-30.

Kunin CM, McCormack RC. An epidemiology study of bacteriuria and blood pressure among nuns and working women. New Eng J Med 1968; **278**: 635-42.

Kushner L, Chen Y, Desautel M, Moak S, Greenwald R, Badlani G. Collagenase activity is elevated in conditioned media from fibroblasts of women with pelvic floor weakening. Neurourol Urodyn 1999; **18(4)**: 282-3.

Lagro-Janssen TLM, Debruyne FMJ, Smits AJA. Controlled trial of pelvic floor exercises in the treatment of stress incontinence in general practice. Br J General Practice 1991a; **41**: 445-9.

Lagro-Janssen FM, Debruyne FMJ, Van Weel C. Value of a patient's case history in diagnosing urinary incontinence in General Practice. Br J Urol 1991b; **67**: 569-72.

Larsson G, Victor A. Micturition patterns in a healthy female population, studied with a frequency/volume chart. Scan J Urol Nephrol Suppl 1988; **4**: 53-7.

Lasegue C. De l'anorexie hysterique. Arch Gen de Med 1873; 385.

Lenton EA. Progressive changes in LH and FSH and the LH:FSH ratio in women throughout reproductive life. Maturitas 1988; **10**: 35-43.

Lewis L, Warrell DW. Detrusor instability associated with menstruation. Case report. Br J Obstet Gynaecol 1989; **96**: 737-8.

Lincoln J, Burnstock G. Autonomic innervation of the urinary bladder and urethra. In: Maggi CA, editor. Nervous control of the urogenital system. London: Harwood academic publishers, 1993: 33-68.

Lindgren R, Mattsson LA, Andersson K, Lagrelius A, et al. Transvaginal ultrasonography and endometrial histology in peri- and postmenopausal women on hormone replacement therapy. Br J Obstet Gynaecol 1999; **106(5)**: 421-6.

Lindsay R, Hart DM. Failure of response of menopausal vasomotor symptoms of clonidine. Maturitas 1999; **1**: 21-5.

Ly WC, Chan RKT, Lee EJC, Kumarasinghe G. Urinary tract infections in patients with diabetes mellitus. Journal of Infection 1992; **24**: 169-74.

Lye M. Defining and treating urinary tract infections. Geriatrics 1978; **33**: 71-7.

MacLaren DM. Virulence factors of proteus. In: Brumfitt W, Hamilton-Miller JMT, Bailey RR, editors. Urinary tract infections. Cambridge: University Press, 1998: 76-85.

Maggi A, Perez J. Role of female gonadal hormones in the CNS. Life Sci 1985; **37**: 893-906.

Maggi CA. Prostanoids as local modulators of reflex micturition. Pharmacol Res 1992; **25**: 13-20.

Malone Lee J, Waheda I. The characterisation of detrusor contractile function in relation to old age. Br J Urol 1993; **72**: 873-80.

Marrie TJ, Harding GKM, Ronald AR. Anaerobic and aerobic urethral flora in healthy females. Journal of Clinical Microbiology 1978; **8**: 67-72.

Matthews BJ, Lacey JH, Cleeve H. Premature loss of bone in chronic anorexia nervosa. Br Med J Clin Res Ed 1985; **290**: 1431

McCallin PF, Taylor ES, Whitehead RW. A study of the changes in the urinary sediment during the menstrual cycle. Am J Obstet Gynecol 1950; **60**: 64-74.

McClain CJ, Humphries LL, Hill KK, et al. Gastrointestinal and nutritional aspects of eating disorders. J Am Coll Nutr 1993; **12(4)**: 466-74.

McMurray G, Brading AF. The mechanism of action of drugs affecting the lower urinary tract in the treatment of female urinary incontinence. The Journal of the British Menopause Society 1998; 4(3): 114-21.

Miall WE, Kass EH, Ling J, Stuart KL. Factors influencing arterial pressure in the general population. BMJ 1962; 2: 497-502.

Miller JM, Ashton Miller JA, DeLancey JOL. A pelvic muscle precontraction can reduce cough-related urine loss in selected women with mild SUI. J Am Geriatr Soc 1998; 46(7): 870-4.

Mitchell JE, Seim HC, Colon E, et al. Medical complications and medical management of bulimia. Ann Int Med 1987; 107(1): 71-7.

Moisey CU, Stephenson TP, Brendler CB. The urodynamic and subjective results of treatment of detrusor instability with oxybutynin chloride. Br J Urol 1980; 52: 472-5.

Molander U, Milsom I, Ekelund P, et al. A health care program for the investigation and treatment of elderly women with urinary incontinence and related urogenital symptoms. Acta Obstet Gynecol Scand 1991; 70: 137-42.

Monane M, Gurwitz J, Lipsitz LA, Glynn RJ, et al. Epidemiologic and Diagnostic Aspects of Bacteriuria: A Longitudinal Study in Older Women. J Am Geriatr Soc 1995; 43: 618-22.

Monga AK, Robinson D, Stanton SL. Periurethral injections for genuine stress incontinence: a 2-year follow up. Br J Urol 1999; 76: 156-60.

Morton MS, Griffiths K. Phytoestrogens and cancer. In: Studd JW, editor. The modern management of the menopause. Annual review 1998. Carnforth, Lancs: Parthenon, 1998: 81-92.

Muldoon MF, Barger SD, Flory JD, Manuck SB. What are quality of life measurements measuring? BMJ 1998; 316: 542-5.

Nicolle LE, Harding GK, Preiksaitis J, Ronald AR. The association of urinary tract infection with sexual intercourse. J Infect Dis 1982; **146**: 579-83.

Nilsson K, Heimer G. Low dose oestradiol in the treatment of urogenital oestrogen deficiency - a pharmacokinetic and pharmacodynamic study. Maturitas 1992; **15**: 121-7.

Norton PA, MacDonald LD, Sedgwick PM, Stanton SL. Distress and delay associated with urinary incontinence, frequency, and urgency in women. BMJ 1988; **297**: 1187-9.

Norton PA. Prevalence and social impact of urinary incontinence in women. Clinical Obstet Gynecol 1990; **33(2)**: 295-7.

O'Brien J, Austin M, Sethi P, O'Boyle P. Urinary incontinence: prevalence, need for treatment, and effectiveness of intervention by nurse. BMJ 1991; **303**: 1308-12.

O'Dowd MJ, Philipp EE. The menopause. In: History of Obstetrics and Gynaecology. Carnforth, Lancs: Parthenon: 1994: 317-328.

Oliveria SA, Klein RA, Reed JI, Cirillo PA, et al. Estrogen Replacement Therapy and Urinary Tract Infections in Postmenopausal Women Aged 45-89. Menopause, The Journal of the North American Menopause Society 1997; **5(1)**: 4-8.

Orlander JD, Jick SS, Dean AD, Jick H. Urinary tract infections and estrogen use in older women. J Am Geriatr Soc 1992; **40(8)**: 817-20.

Parsons CL, Schmidt JD. Control of recurrent lower urinary tract infections in postmenopausal women. J Urol 1982; **128**: 1224-6.

Paterson MEL, Wade-Evans T, Sturdee D. Endometrial disease after treatment with oestrogens and progestogens in the climacteric. BMJ 1980; **280**: 822-4.

Penotti M, Farina M, Sironi L, Miglierina L, Castiglioni E, Gabrielli L, Vignali M. Long term effects of postmenopausal hormone replacement therapy on pulsatility index

of internal carotid and middle cerebral arteries. Menopause, The Journal of the North American Menopause Society 1997; **4(2)**: 101-4.

Perucchini D, DeLancey JOL, Patane L, Kataria T, Peschers U, Ashton Miller JA. The number and diameter of striated muscle fibres in the female urethra. Neurourol Urodyn 1997; **16(5)**: 405-6.

Pirke KM, Platte P. Neurobiology of eating disorders in adolescence. In: Steinhausen HC, editor. Eating Disorders in Adolescence. New York: Walter de Gruyter, 1995: 171-89.

Plevnik S. A new method for testing and strengthening of pelvic floor muscles. Proceedings of the 15th Annual General Meeting, International Continence Society. 1985; 267.

Price KR, Fenwick GR. Naturally occurring oestrogens in food - a review. Food Add Contam 1985; **2**: 73-106.

Privette M, Cade R, Peterson J, Mars D. Prevention of recurrent urinary tract infections in postmenopausal women. Nephron 1988; **50**: 24-7.

Rathner G, Messner K. Detection of eating disorders in a small rural town: an epidemiological study. Psychological Medicine 1993; **23**: 175-84.

Raz S, Ziegler M, Laine M. The effect of progesterone on the adrenergic receptors of the urethra. Br J Urol 1973; **45**: 131-5.

Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. New Eng J Med 1993; **329**: 753-6.

Rekers H, Drogendijk AC, Valkenburg H, Riphagen F. Urinary incontinence in women from 35 to 79 years of age: prevalence and consequences. Eur J Obstet Gynecol Reprod Biol 1992; **43**: 229-34.

Report of a WHO Scientific Group. Research on the menopause in the 1990's. WHO Technical Report Series 866. Geneva: World Health Organisation, 1994.

Restorick JM, Mundy AR. The density of cholinergic and alpha and beta adrenergic receptors in normal and hyper-reflexic human detrusor. Br J Urol 1989; **63**: 32-5.

Rollema HJ, Van Mastrigt R, Ambergen AW, et al. Detrusor instability in benign prostatic hypertrophy (BPH); low incidence by suprapubic filling cystometry. Neurourol Urodyn 1990; **9**: 422-3.

Ronald AR. Sex and urinary tract infections [Editorial]. New Eng J Med 1996; **335(7)**: 511-2.

Rosenzweig BA, Bhatia NN, Nelson AL. Dynamic urethral pressure profilometry pressure transmission ratio. What do the numbers really mean? Obstet Gynecol 1991; **77**: 586-90.

Rud T, Andersson KE, Ulmsten U. Effects of nifedipine in women with unstable bladders. Urol Int 1979; **34**: 421-9.

Rud T. The effects of estrogens and gestogens on the urethral pressure profile in urinary continent and stress incontinent women. Acta Obstet Gynecol Scand 1980; **59**: 265-70.

Rud T, Anderson KE, Asmussen M, et al. Factors maintaining the urethral pressure in women. Invest Urol 1980; **17**: 343-7.

Ryan KG, Engel LI. The interconversion of oestrone and estradiol by human tissue slices. Endocrinology 1953; **52**: 287-91.

Ryan PJ, Harrison R, Blake GM, Fogelman I. Compliance with hormone replacement therapy (HRT) after screening for postmenopausal osteoporosis. Br J Obstet Gynaecol 1992; **99**: 325-8.

Ryhammer AM, Djurhuus JC, Laurberg S, Herman AP. No relationship between self-reported urinary incontinence and pad test weight gain in healthy perimenopausal women. Neurourol Urodyn 1995; **14**: 456-7.

Sacco F, Rigon G, Carbone A, Sacchini D. Terapia estrogenica transvaginale dell'incontinenza urinaria da sforzo. Minerva Ginecologica 1990; **42**: 539-44.

Sadler TW. Urogenital system. In: Langman's medical embryology. Second edition. Baltimore: Williams & Wilkins, 1995, 272-311.

Salmon UL, Walter RI, Gast SH. The use of estrogen in the treatment of dysuria and incontinence in postmenopausal women. Am J Obstet Gynecol 1941; **14**: 23-31.

Samsioe G, Jansson I, Mellstrom D, et al. Occurrence, nature and treatment of urinary incontinence in a 75 year old female population. Maturitas 1985a; **7**: 335-42.

Samsioe G, Jansson I, Mellstrom D, Svanberg A. Urinary incontinence in 75-year old women. Effects of estriol. Acta Obstet Gynecol Scand 1985b; **Suppl 93**: 57.

Sand PK, Richardson DA, Staskin DR, Swift SE, Appell RA, Whitmore KE, Ostergard DR. Pelvic floor electrical stimulation in the treatment of genuine stress incontinence: A multicentre, placebo-controlled trial. Acta Obstet Gynecol Scand 1995; **173(1)**: 72-9.

Sanderson J. An agenda for action on continence services. London: Department of Health, 1991: ML (19)1.

Sanderson PJ. Laboratory Methods. In: Brumfitt W, Hamilton-Miller JMT, Bailey RR, editors. Urinary Tract Infections. Cambridge: University Press, 1998: 1-15.

Sanford JRA. Tolerance of debility in elderly dependents by supporters at home: its significance for hospital practice. BMJ 1975; **3**: 471.

Schiff I, Sela HK, Cramer D, et al. Endometrial hyperplasia in women on cyclic or continuous oestrogen regimes. Fertil Steril 1982; **27**: 79-82.

Schneider MA, Brotherton PL, Hailes J. The effect of exogenous oestrogens on depression in menopausal women. Med J Aust 1977; **2**: 162-3.

Screiter F, Fuchs P, Stockamp K. Estrogenic sensitivity of alpha receptors in the urethral musculature. Urol Int 1976; **31**: 13-9.

Semmens JP, Wagner G. Estrogen deprivation and vaginal function in postmenopausal women. JAMA 1982; **248**: 445.

Semmens JP, Tsai CC, Semmens EC, et al. Effects of estrogen therapy on vaginal physiology during the menopause. Obstet Gynecol 1985; **66**: 15-8.

Shapiro AK. A historic and heuristic definition of placebo. Psychiatry 1964; **27**: 52-8.

Shapiro E. Effect of oestrogens on the weight and muscarinic receptor density of the rabbit bladder and urethra. J Urol 1986; **135**: 1084-7.

Shenfield OZ, Blackmore PF, Morgan CW, Schlossberg SM, Jordan GH, Ratz PH. Rapid effects of estradiol and progesterone on tone and spontaneous rhythmic contractions of the rabbit bladder. Neurourol Urodyn 1998; **17(4)**: 408-9.

Sherwin BB. Affective changes with estrogen and androgen replacement therapy in surgically menopausal women. J Affect Disord 1988; **14**: 177-87.

Shimonovitz S, Monga AK, Stanton SL. Does the menstrual cycle influence cystometry? Int Urogynecol J 1997; **8**: 213-6.

Sichieri R, Everhart JE, Hubbard VS. Relative weight classifications in the assessment of underweight and overweight in the United States. Int J Obes 1991; **16**: 303-12.

Smith PJB. The effect of oestrogens on bladder function. In: Campbell S, editor. Management of the Menopause and Postmenopausal Years. Lancaster: MTP Press, 1976: 291-298.

Smith ARB, Hosker GL, Warrell DW. The role of partial denervation of the pelvic floor in the aetiology of genito-urinary prolapse and stress incontinence of urine. Br J Obstet Gynaecol 1989; **96**: 24-8.

Smith P. Estrogens and the urogenital tract. Acta Obstet Gynecol Scand 1993; **72**: 1-26.

Smith SS. Hormones, mood and neurobiology-a summary. In: Berg G, Hammar M, editors. The modern management of the menopause. Carnforth, Lancs: Parthenon Publishing, 1993: 204.

Smith P, Heimer G, Ulmsten U. Oestradiol releasing vaginal ring for the treatment of postmenopausal urogenital atrophy. Maturitas 1993; 16: 145-154.

Soloman C, Panagotopoulos P, Oppenheim A. The use of urinary sediment as an aid in endocrinological disorders in the female. Am J Obstet Gynecol 1958; **76**: 56-60.

Sorensen S, Knudsen UB, Kirkeby HJ, Djurhuus JC. Urodynamic investigations in healthy fertile females during the menstrual cycle. Scan J Urol Nephrol Suppl 1988; **114**: 28-34.

Stamey TA, Kaufman MF. Studies of introital colonization in women with recurrent urinary infections. I. The role of vaginal pH. J Urol 1975; **114**: 264-7.

Stamey TA, Timothy MM. Studies of introital colonization in women with recurrent urinary infections. III. Vaginal glycogen concentrations. J Urol 1975; **114**: 268-70.

Stanton SL, Kerr-Wilson R, Harris VG. The incidence of urological symptoms in normal pregnancy. Br J Obstet Gynaecol 1980; **87**: 897-900.

Steadman R, Topley N. The virulence of *Escherichia Coli* in the urinary tract. In: Brumfitt W, Hamilton-Miller JMT, Bailey RR, editors. Urinary tract infections. Cambridge: University Press, 1998: 37-58.

Strober M. Personality and symptomatological features in young, non chronic anorexia nervosa patients. J Psychosom Res 1980; **24**: 353-9.

Strober M, Morrell W, Burroughs J, Salkin B, Jacobs C. A controlled family study of anorexia nervosa. Journal of Psychiatric Research 1985; **19**: 239-46.

Strom BL, Collins M, West SL. Sexual activity, contraception use, and other risk factors for symptomatic and asymptomatic bacteriuria. Annals of International Medicine 1987; **107**: 816-23.

Studd JW, Magos A. Hormone pellet implantation for the menopause and premenstrual syndrome. Obstet Gynecol Clin North Am 1987; **14(1)**: 229-49.

Studd JW, Baber R. The Menopause. In: Shaw R, Soutter P, Stanton SL, editors. Gynaecology. Edinburgh: Churchill Livingstone, 1992: 341-354.

Sturdee D, Wade-Evans T, Pterson MEL, Thom M, Studd JW. Relations between bleeding pattern, endometrial histology and oestrogen treatment in postmenopausal women. BMJ 1978; **1**: 1575-7.

Sturdee D. Irregular bleeding (Problems with HRT minisymposium). The Diplomate 1998; **5(1)**: 29-32.

Sultana CJ, Walters MD. Estrogen and urinary incontinence in women. Maturitas 1995; **20**: 129-38.

Susset JG, Servot-Viguier D, Lamy F, et al. Collagen in 155 human bladders. Invest Urol 1978; **16**: 204-6.

Svanberg A. The gerontological and geriatric study in Goteborg, Sweden. Acta Med Scand 1977; **611**: 1-37.

Swift SE, Ostergard DR. Effects of progesterone on the urinary tract. Int Urogynecol J 1993; **4**: 232-6.

Swithinbank LV, Vestey S, Abrams P. Nocturnal polyuria in community dwelling women. Neurourol Urodyn 1998; **17(4)**: 314-5.

Szmukler GI. The Epidemiology of anorexia nervosa and bulimia. Journal of Psychiatric Research 1985; **19**: 143-53.

Takala J, Jousimes H, Sievers K. Screening for and treatment of bacteriuria in a middle aged female population. Acta Med Scand 1977; **202**: 69-73.

Taylor MC, Bates CP. A double-blind crossover trial of baclofen-a new treatment for the unstable bladder syndrome. Br J Urol 1979; **51**: 504-5.

Tessier J, Schick E. Does urethral instrumentation affect uroflowmetry measurements. Br J Urol 1990; **65**: 261-3.

Thienemann M, Steiner H. Family environment of eating disordered and depressed adolescents. International Journal of Eating Disorders 1993; **14**: 43-8.

Thom MH, White PJ, Williams RM, et al. Prevention and treatment of endometrial disease in climacteric women receiving oestrogen therapy. Lancet 1979; **2(8140)**: 455-7.

Thomas TM, Plymat KR, Blannin J, Meade TW. Prevalence of urinary incontinence. Br Med J 1980; **281**: 1243-5.

Toozs-Hobson P, Cardozo L. Interstitial cystitis-still an enigma after 80 years. Br J Obstet Gynaecol 1996; **103(7)**: 621-4.

Treasure JL, Fogelman I, Russell GF. Osteopenia of the lumbar spine and femoral neck in anorexia nervosa. Scott Med J 1986; **31**: 206-7.

Tulandi T, Kinch RA, Guyda H, Mazella A, Lal S. Effect of methyldopa on menopausal flushes, skin temperature and luteinizing hormone secretion. Am J Obstet Gynecol 1984; **150**: 709-12.

Turner-Warwick RT, Ashken MH. The functional results of partial subtotal and total cystoplasty with special reference to ureterocaecoplasty, selective sphincterotomy and cystocystoplasty. Br J Urol 1976; **39**: 3-12.

Turner WH, Brading AF. Smooth muscle of the bladder in the normal and diseased state: Pathophysiology, diagnosis and treatment. Pharmacol Ther 1997; **75**: 77-110.

Ulmsten U, Johnson P, Rezapour M. A three-year follow up of tension free vaginal tape for surgical treatment of female stress urinary incontinence. Br J Obstet Gynaecol 1999; **106(4)**: 345-50.

Ulrich L.G., Barlow DH, Sturdee D, et al. Quality of life and patient preference for sequential versus continuous combined HRT: the UK Kliofem multicentre study experience. Int J Gynecol Obstet 1997; **59 (suppl 1)**: S11-7.

Van Geelen JM, Doesburg WH, Thomas CMG. Urodynamic studies in the normal menstrual cycle: the relationship between hormonal changes during the menstrual cycle and the urethral pressure profile. Am J Obstet Gynecol 1981; **141**: 384-92.

Van Hoeken D, Lucas AR, Hoek HW. Epidemiology. In: Hoek HW, Treasure JL, Katzman MA, editors. Neurobiology in the treatment of eating disorders. Chichester: John Wiley and Sons Ltd, 1998: 97-126.

Verbrugge LM. Health diaries. Med Care 1980; **18**: 73.

Versi E, Cardozo LD. Urethral instability: diagnosis based on variations in the maximum urethral pressure in normal climacteric women. Neurourol Urodyn 1986; **5**: 535-41.

Versi E. Discriminant analysis of urethral pressure profilometry data for the diagnosis of genuine stress incontinence. Br J Obstet Gynaecol 1990; **97**: 251-9.

Vetter NJ, Jones DA, Victor CR. Urinary incontinence in the elderly at home. Lancet 1981; **2**: 1275-7.

Wagg AS, Lieu PK, Ding YY. A urodynamic evaluation of age associated changes in urethral function in women with lower urinary tract symptoms. J Urol 1996; **156**: 1984-8.

Walkey FA, Judge TG, Thompson J, Sakari NBS. Incidence of urinary tract infection in the elderly. Scott Med J 1967; **12**: 411-4.

Walter GJ, Vejlsgaard R. Diagnostic catheterisation and bacteriuria in women with urinary incontinence. Br J Urol 1978; **50**: 106-8.

Walter S, Wolf H, Barlebo H, et al. Urinary incontinence in postmenopausal women treated with oestrogen. *Urol Int* 1978; **33**: 135-43.

Walter S, Kjaergaard B, Lose G, et al. Stress urinary incontinence in postmenopausal women treated with oral oestrogen (oestriol) and an alpha-adrenoceptor-stimulating agent (phenylpropanolamine): A randomised double-blind placebo controlled study. Int Urogynecol J 1990; **1**: 74-9.

Wang P, Luthin GR, Ruggieri MR. Muscarinic acetylcholine receptor subtypes mediating urinary bladder contractility and coupling to GTP binding proteins. Journal of Pharmacology and Experimental 1995; **273**: 959-66.

Wein A. Pharmacology of incontinence. Urologic Clinics of North America 1995; **22**: 557-77.

Welshons WV, Lieberman ME, Gorshi J. Nuclear localization of unoccupied oestrogen receptors. Nature 1984; **307**: 747.

Whitaker A, Johnson J, Schaffer D, et al. Uncommon troubles in young people: prevalence estimates of selected psychiatric disorders in a non referred adolescent population. Arch Gen Psychiatry 1990; **47**: 487-96.

Whitehead MI. The effect of oestrogens and progestogens on the postmenopausal endometrium. Maturitas 1987; **1**: 87-98.

Whitehouse AM, Button EJ. Prevalence of eating disorders in three Cambridge general practices: hidden and conspicuous morbidity. Br J General Practice 1988; **42**: 57-60.

Whiteside CG, Arnold GP. Persistent primary enuresis: a urodynamic assessment. BMJ 1975; **1**: 364-9.

Wilbush J. La Menespausie - the birth of a syndrome. Maturitas 1979; **1**: 145-51.

Wilkes HC, Meade TW. Hormone replacement therapy in general practice: a survey of doctors in the MRC's general practice framework. BMJ 1991; **302**: 1317-20.

Williamson DA, Cubic BA, Gleaves DH. Equivalence of body image disturbances in anorexia and bulimia nervosa. J Ab Psychol 1993; **102**: 1-4.

Wilson GT, Heffernan K, Black CM. Eating disorders. In: Mash EJ, Barkley RA, editors. Child Psychopathology. New York: The Guilford Press, 1996: 541-547.

Wilson PD, Barker G, Barnard RJ, et al. Steroid hormone receptors in the female lower urinary tract. Urol Int 1984; **39**: 5-8.

Wilson PD, Faragher B, Butler B, et al. Treatment with oral piperazine sulphate for genuine stress incontinence in postmenopausal women. Br J Obstet Gynaecol 1987; **94**: 568-74.

Wise BG, Cardozo L, Cutner A, Kelleher CJ, Burton G. Maximal electrical stimulation: an acceptable alternative to anticholinergic therapy. Int Urogynecol J 1992; **3(3)**: 270.

Wolf H, Wandt H, Jonat W. Immunohistochemical evidence of oestrogen and progesterone receptors in the female lower urinary tract and comparison with the vagina. Gynecol Obstet Invest 1991; **32**: 227-31.

Woodburne RT. The ureter ureterovesical junction and vesical trigone. Anatomy Record 1965; **151**: 243-9.

Wyman JF, Harkins SW, Choi SC, Taylor JR, Fantl JA. Psychosocial impact of urinary incontinence in women. Obstet Gynecol 1987; **71**: 812-7.

Wyman JF, Sung CC, Harkins SW, Wilson MS, Fantl JA. The urinary diary in the evaluation of incontinent women: a test-retest analysis. Obstet Gynecol 1988; **71**: 812-7.

Wyman JF, Harkins SW, Fantl JA. Psychosocial impact of urinary incontinence in the community dwelling population. Am Geriatric Society 1990; **38**: 282-8.

Yamaguchi O, Shisido K, Tamura K, Ogawa T, Fujimura T. Evaluation of mRNA encoding muscarinic receptor subtypes in human detrusor muscle. Neurourol Urodyn 1994; **13**: 464-5.

APPENDIX

1. King's College Hospital Frequency - Volume Chart
2. Visual Analogue Symptom Score
3. King's Health Questionnaire and Scoring System
4. EAT 26 Questionnaire
5. Menstrual Status and Urinary Symptom Questionnaire used in Chapter 9
6. Eating Disorder Study Information Sheet and Consent Form used in Chapter 10
7. Oestradiol Implant Study Information Sheet and Consent Form used in Chapter 12
8. Doctor Administered Urinary Symptom Questionnaire used in Chapter 12

King's College Hospital

Frequency - Volume Chart

KINGS COLLEGE HOSPITAL

URODYNAMICS DEPARTMENT

FREQUENCY VOLUMÉ CHART

IMPORTANT - PLEASE READ CAREFULLY

It is imperative that you fill in the chart overleaf as carefully as possible during the five days before you come for your bladder test. It is designed to give us an idea of your fluid intake and urine output and leakage. This assists us greatly in the diagnosis of your condition.

For each day record how much you drink (metric, ie - mls if possible) and when you drink it (put the volume in the square provided for that time). If you always drink from the same cup then you need only measure how much it holds once and put that value down every time you drink from it.

When you go to the toilet, measure the urine you pass using a jug. If possible, record the volume in millilitres rather than fluid ounces, and again record it next to the right time.

Every time you leak, put a 'W' for wet in the column provided.

When you go to bed, put a line on the chart next to the right time so that we can tell how many times you have to get up at night to pass water.

If you are unable to fill the chart in properly every day because of other commitments, please try to fill it in accurately for at least two days and record the frequency of passing water and leaking by ticking the correct box for the rest of the time.

For example:

Day One

Time	In	Out	Wet
6.00am			
7.00am		400	
8.00am	150		
9.00am		150	W
10.00am			
11.00am	150		
12.00pm			
1.00pm	200		W
2.00pm		300	

Urine passed = 400ml at 7.00am
Drank tea = 150ml at 8.00am
Wet at 9.00am
Urine passed = 150ml at 9.30am

	Day 1			Day 2			Day 3			Day 4			Day 5		
Time	In	Out	Wet	In	Out	Wet	In	Out	Wet	In	Out	Wet	In	Out	Wet
6 am															
7 am															
8 am															
9 am															
10 am															
11 am															
12 pm															
1 pm															
2 pm															
3 pm															
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8 pm															
9 pm															
10 pm															
11 pm															
12 am															
1 am															
2 am															
3 am															
4 am															
5 am															

Visual Analogue Symptom Score

VISUAL ANALOGUE SYMPTOM SCORE

Name _____

Number ☐☐☐ 1-3

Visit ☐ 4

Date ☐☐☐☐☐☐ 5-10

Frequency (Daytime)

Normal ——————— Very frequent ☐☐☐

Nocturia (Night)

Normal ——————— Very frequent ☐☐☐

Stress incontinence

Not a problem ——————— Very severe ☐☐☐

Urgency

Not a problem ——————— Very severe ☐☐☐

Urge incontinence

Not a problem ——————— Very severe ☐☐☐

Bedwetting

Not a problem ——————— Very severe ☐☐☐

Stream

Normal ——————— Very slow ☐☐☐

Complete emptying

Always ——————— Never ☐☐☐

King's Health Questionnaire and Scoring System

KING'S HEALTH QUESTIONNAIRE

1993

Name _____

Age _____ years

Todays date ___/___ 199

Office use

How would you describe your health at present ?

Please tick one answer

Very good	○
Good	○
Fair	○
Poor	○
Very poor	○

5

How much do you think your bladder problem affects your life ?

Please tick one answer

Not at all	○
A little	○
Moderately	○
A lot	○

4

Please turn the page

We would like to know what your bladder problems are and how much they affect you. From the list below choose ONLY THOSE PROBLEMS that you have at present. LEAVE OUT those that do not apply to you.

How much do they affect you ?

To choose please tick ◯	A Little	Moderately	A lot	
FREQUENCY; going to the toilet very often.	◯	◯	◯	☐
NOCTURIA; getting up at night to pass urine.	◯	◯	◯	☐
URGENCY; a strong and difficult to control desire to pass urine.	◯	◯	◯	☐
URGE INCONTINENCE; urinary leakage associated with a strong desire to pass urine.	◯	◯	◯	☐
STRESS INCONTINENCE; urinary leakage with physical activity eg coughing, sneezing, running.	◯	◯	◯	☐
NOCTURNAL ENURESIS; wetting the bed at night.	◯	◯	◯	☐
INTERCOURSE INCONTINENCE; urinary leakage with sexual intercourse.	◯	◯	◯	☐
FREQUENT WATERWORKS INFECTIONS;	◯	◯	◯	☐
BLADDER PAIN;	◯	◯	◯	☐
Difficulty PASSING URINE	◯	◯	◯	☐
OTHER SPECIFY; _____	◯	◯	◯	☐

Please turn the page

Office use	☐ +	☐ +	☐

Below are some daily activities that can be affected by bladder problems. How much does your bladder problem affect you ?
We would like you to answer every question. Simply tick the circle that applies to you.

ROLE LIMITATIONS	Not at all	Slightly	Moderately	A lot
To what extent does your bladder problem affect your household tasks (eg cleaning, shopping etc)	○	○	○	○
Does your bladder problem affect your job, or your normal daily activities outside the home?	○	○	○	○

PHYSICAL/SOCIAL LIMITATIONS	Not at all	Slightly	Moderately	A lot
Does your bladder problem affect your physical activities (eg going for a walk, run, sport, gymn etc)?	○	○	○	○
Does your bladder problem affect your ability to travel?	○	○	○	○
Does your bladder problem limit your social life ?	○	○	○	○
Does your bladder problem limit your ability to see/visit friends ?	○	○	○	○

PERSONAL RELATIONSHIPS	Not applicable	Not at all	Slightly	Moderately	A lot
Does your bladder problem affect your relationship with your partner?	○	○	○	○	○
Does your bladder problem affect your sex life?	○	○	○	○	○
Does your bladder problem affect your family life?	○	○	○	○	○

Please turn the page

Office use □□ □□ □□ □□□

EMOTIONS	Not at all	Slightly	Moderately	Very much
Does your bladder problem make you feel depressed?	○	○	○	○
Does your bladder problem make you feel anxious or nervous?	○	○	○	○
Does your bladder problem make you feel bad about yourself?	○	○	○	○

SLEEP / ENERGY	Never	Sometimes	Often	All the time
Does your bladder problem affect your sleep ?	○	○	○	○
Do you feel worn out / tired?	○	○	○	○

Do you do any of the following?;	If so how much ?			
	Never	Sometimes	Often	All the time
Wear pads to keep dry?	○	○	○	○
Be careful how much fluid you drink?	○	○	○	○
Change your underclothes when they get wet?	○	○	○	○
Worry in case you smell?	○	○	○	○
Get embarassed because of your bladder problem ?	○	○	○	○

Office use ☐☐☐ ☐☐ ☐☐☐☐

THANKYOU, NOW CHECK THAT YOU HAVE ANSWERED ALL THE QUESTIONS

King's Health Questionnaire, Version 7.

Kings Health Questionnaire

	SCALE	SCORE
PART I		
General Health Perception		
1. How would you describe your health at present ?	Very good	1
	Good	2
	Fair	3
	Poor	4
	Very poor	5
Incontinence Impact		
2. How much do you think your bladder problem affects your life ?	Not at all	1
	A little	2
	Moderately	3
	A Lot	4
PART II		
Role Limitations		
3a. To what extent does your bladder problem affect your household tasks (eg cleaning, shopping etc) ?	Not at all	1
3b. Does your bladder problem affect your job, or your normal daily activities outside the home ?	Slightly	2
	Moderately	3
	A lot	4
Physical limitations		
4a. Does your bladder problem affect your physical activities (eg going for a walk, run, sport, gym etc) ?		
4b. Does your bladder problem affect your ability to travel ?		
Social limitations		
4c. Does your bladder problem restrict your social life ?		
4d. Does your bladder problem limit your ability to see / visit friends ?		

Personal Relationships

5a. Does your bladder problem affect your relationship with your partner ?	Not applicable	0
5b. Does your bladder problem affect your sex life ?	Not at all	1
5c. Does your bladder problem affect your family life ?	Slightly	2
	Moderately	3
	A lot	4

Emotions

6a. Does your bladder problem make you feel depressed ?	Not at all	1
6b. Does your bladder problem make you feel anxious or nervous ?	Slightly	2
6c. Does your bladder problem make you feel bad about yourself ?	Moderately	3
	Very much	4

Sleep / Energy

7a. Does your bladder problem affect your sleep ?	Never	1
7b. Do you feel worn out or tired ?	Sometimes	2
	Often	3
	All the time	4

Severity Measures

Do you do any of the following; if so how much ?

8a - Wear pads to keep dry ?	Never	1
8b - Be careful how much fluid you drink ?	Sometimes	2
8c - Change your underclothes when they get wet ?	Often	3
8d - Worry in case you smell ?	All the time	4
8e - Get embarrassed because of your bladder problem ?		

PART III

We would like to know what your bladder problems are and how much they affect you. From the list below choose only those problems that you have at present. Leave out those that do not apply to you.

- o ***Frequency*** : Going to the toilet very often.
- o ***Nocturia*** : Getting up at night to pass urine.
- o ***Urgency*** : A strong and difficult to control desire to pass urine.
- o ***Urge incontinence*** : Urinary leakage associated with a strong desire to pass urine.
- o ***Stress incontinence*** : Urinary leakage with physical activity, eg coughing, sneezing, running.
- o ***Nocturnal enuresis*** : Wetting the bed at night.
- o ***Intercourse incontinence*** : Urinary leakage with sexual intercourse.
- o ***Frequent waterworks infections***
- o ***Bladder pain***
- o ***Difficulty passing urine***
- o ***Other (Please specify)***

Scale	Score
A little	= 1
Moderately	= 2
A lot	= 3
Omitted	= 0

To Calculate Scores

1. General Health perceptions

Score = ((Score to Qu1 - 1)/4) x 100

2. Incontinence Impact

Score = ((Score to Qu 2 - 1)/3) x 100

3. Role Limitations

Score = (((Scores to Qu 3a+3b) -2) /6) x 100

4. Physical limitations

Score = (((Score to Qu 4a+4b) - 2) /6) x 100

5. Social limitations

Score = (((Score to Qu 4c+4d+5c) - 3) /9) x 100 **

** If score to Qu 5c >= 1, If 0 then ..-2) / 6) x 100

6. Personal Relationships

Score = (((Score to Qu5a+5b) - 2) /6) x 100 ***

** If score to Qu 5a+5b >= 2,
If Qu 5a+5b = 1; ..... -1) /3) x 100
If Qu 5a+5b = 0; ..... treat as missing value (Not applicable)

7. Emotions

Score = (((Score to Qu 6a+6b+6c) - 3) /9) x 100

8. Sleep / Energy

Score = (((Score to Qu 7a+7b) -2) /6) x 100

9. Severity Measures

Score = (((Score to Qu 8a+8b+8c+8d+8e) - 5) /15) x 100

EAT 26 Questionnaire

EAT - 26

Name: ..... Date: .....

INSTRUCTIONS

Please place an (X) under the column which applies best to each of the numbered statements. All of the results will be strictly confidential. Most of the questions directly relate to food or eating, although other types of questions ave been included. Please answer each question carefully. Thank you.

ALWAYS	USUALLY	OFTEN	SOMETIMES	RARELY	NEVER	
( )	( )	( )	( )	( )	( )	1. Am terrified about being overweight
( )	( )	( )	( )	( )	( )	2. Avoid eating when I am hungry
( )	( )	( )	( )	( )	( )	3. Find myself preoccupied with food
( )	( )	( )	( )	( )	( )	4. Have gone on eating binges where I feel that I may not be able to stop
( )	( )	( )	( )	( )	( )	5. Cut my food into small pieces
( )	( )	( )	( )	( )	( )	6. Aware of the calorie content of foods that I eat
( )	( )	( )	( )	( )	( )	7. Particularly avoid foods with a high carbohydrate content (e.g. bread, rice, potatoes, etc.)
( )	( )	( )	( )	( )	( )	8. Feel that others would prefer if I ate more
( )	( )	( )	( )	( )	( )	9. Vomit after I have eaten
( )	( )	( )	( )	( )	( )	10. Feel extremely guilty after eating
( )	( )	( )	( )	( )	( )	11. Am preoccupied with a desire to be thinner
( )	( )	( )	( )	( )	( )	12. Think about burning up calories when I exercise
( )	( )	( )	( )	( )	( )	13. Other people think that I am too thin
( )	( )	( )	( )	( )	( )	14. Am preoccupied with the thought of having fat on my body
( )	( )	( )	( )	( )	( )	15. Take longer than others to eat my meals
( )	( )	( )	( )	( )	( )	16. Avoid foods with sugar in them
( )	( )	( )	( )	( )	( )	17. Eat diet foods
( )	( )	( )	( )	( )	( )	18. Feel that food controls my life
( )	( )	( )	( )	( )	( )	19. Display self-control around food
( )	( )	( )	( )	( )	( )	20. Feel that others pressure me to eat
( )	( )	( )	( )	( )	( )	21. Give too much time and thought to food
( )	( )	( )	( )	( )	( )	22. Feel uncomfortable after eating sweets
( )	( )	( )	( )	( )	( )	23. Engage in dieting behaviour
( )	( )	( )	( )	( )	( )	24. Like my stomach to be empty
( )	( )	( )	( )	( )	( )	25. Enjoy trying new rich foods
( )	( )	( )	( )	( )	( )	26. Have the impulse to vomit after meals

Menstrual Status and Urinary Symptom

Questionnaire used in Chapter 9

THE DEPARTMENT OF UROGYNAECOLOGY
KING'S COLLEGE HOSPITAL LONDON

Professor Linda Cardozo

THE EFFECT OF HORMONES ON THE BLADDER

We are trying to find out what effect the female hormones oestrogen and progesterone have on the bladder. These hormones are found naturally in all women and are important in the control of fertility, periods and bone strength. After the menopause the level of oestrogen falls, unless Hormone Replacement Therapy (HRT) is being taken. We think that this fall may be important in the development of some bladder problems and urinary symptoms.

We would be most grateful if you would complete the following questionnaire and return it to the X-ray receptionist. Thank you for your help which is much appreciated.

YOUR NAME _____ **AGE** _____

TODAY'S DATE _____

HOW MANY CHILDREN HAVE YOU HAD? _____

PLEASE TICK THE BOX WHICH APPLIES TO YOU

QUESTION 1

What do you think is the <u>main</u> cause of your bladder problems?

Please tick **<u>ONE</u>** box only

- Having children ☐
- Menopause / stopping periods ☐
- A hysterectomy ☐
- An operation other than a hysterectomy ☐
- Medications / tablets ☐
- Cold weather ☐
- Mental stress ☐
- Another reason (please state) _____

QUESTION 2

Which of the following treatments have you had in the past for your bladder problem?

Please tick **MORE THAN ONE** box if you wish

- An operation ☐
- Pelvic floor exercises ☐
- Electrical stimulation ☐
- Tablets ☐
- Bladder retraining ☐
- No treatment so far ☐
- Other (please state) _____

_____

_____

QUESTION 3

Are you taking any tablets or medications at the moment? **Yes** ☐ **No** ☐

If **YES**, what tablets or medications are you taking?

- _____
- _____
- _____
- _____
- _____

QUESTION 4 **Are you still having periods?** **Yes** ☐ **No** ☐

If YES (A) When was your last period? _____

(B) Are your periods regular? **Yes** ☐ **No** ☐

(C) Does your bladder problem change during the month? **Yes** ☐ **No** ☐

If **YES**, at what time of the month do your bladder symptoms bother you the most?

Please tick **ONE** box only

- During a period ☐
- Just after a period ☐
- In the middle of the month ☐
- Just before a period ☐
- Other time (please state) _____

If NO (A) When did your periods stop? _____

(B) Why did you stop having periods?

- Menopause ☐
- Hysterectomy ☐
- Contraceptive pill / injection ☐
- Another reason (please state) _____

(C) If your periods stopped because you went through the **menopause**, how are your bladder problems now compared to the time when you were having periods?

- Much better ☐
- Better ☐
- The same ☐
- Worse ☐
- Much worse ☐

QUESTION 5

Have you had a hysterectomy (removal of your womb) **Yes** ☐ **No** ☐

If YES (A) How old were you when you had a hysterectomy? _____

(B) How was the operation done? Through a cut in the tummy ☐

Through the vagina ☐

Key hole surgery ☐

(C) Were your ovaries removed at the same time? **Yes** ☐ **No** ☐

If YES, how many ovaries were removed? One ☐

Two ☐

Unsure ☐

(D) Did you start Hormone Replacement Therapy (HRT) within 2 months of your hysterectomy? **Yes** ☐ **No** ☐

(E) Do you think your bladder problems were caused by your hysterectomy? **Yes** ☐ **No** ☐

QUESTION 6

Have you ever taken the contraceptive pill? **Yes** ☐ **No** ☐

Are you taking the pill at the moment? **Yes** ☐ **No** ☐

QUESTION 7

Have you ever taken Hormone Replacement Therapy (HRT)? **Yes** ☐ **No** ☐

Are you taking HRT at the moment? **Yes** ☐ **No** ☐

If **YES** what sort of HRT are you taking?

- Tablets ☐
- Patches ☐
- Implants ☐
- Cream which goes into the vagina ☐
- Cream which is rubbed on the skin ☐
- Other (Please state) _____

QUESTION 8

Are you:

- White ☐
- Black African ☐
- Black Afro-Caribbean ☐
- Asian ☐
- Chinese ☐
- Other (please state) _____

If you would like to make any further comments please write below.

Thank you for your help. Please return this questionnaire to the X-ray receptionist.

Eating Disorder Study

Information Sheet and Consent Form

used in Chapter 10

URINARY SYMPTOMS AND EATING DISORDERS

Information for Patients

BACKGROUND

Women start to ovulate (release an egg from the ovary) when their body reaches a certain weight; most women will then have periods. This normally occurs in the teenage years. If a person looses weight, perhaps because they are unwell or have not eaten enough, ovulation and periods may stop. At the same time the level of the female hormone oestrogen can fall to a very low level.

Women who have gone through the menopause, and therefore have a low oestrogen level, have an increased risk of bladder symptoms. We are trying to find out if women with eating disorders, such as anorexia or bulimia, also have similar bladder problems.

WHAT DOES THE STUDY INVOLVE

If you agree to take part you will be asked to complete two questionnaires. The first asks about your view of your weight and how much you eat. The second asks about your bladder, any symptoms it may give you and what affect they have on your Quality of Life. You will be asked to give a sample of your urine and blood so that we can measure your hormone levels. Women will also be asked if they would be prepared to have a bladder test done at King's College Hospital but this is an optional part of the study.

To make the research scientific, we are trying to compare the results from women who have an eating disorder with women who eat normally. We hope the results will help us to improve the treatment we offer to women with both bladder problems and eating problems.

If you would like to ask any questions about the study please feel free to do so.

Dr Sarah Majid

Dr Janet Treasure

Department of Psychiatry

Mr Andrew Hextall

Professor Linda Cardozo

Department of Urogynaecology

January 1998

INFORMED CONSENT FORM

Urinary Symptoms and Eating Disorders

Have you received enough information about the study? YES / NO

Who have you spoken to? Dr / Mr / Ms _____

Do you agree to take part in the study? YES / NO

Patient signature:

Signed _____ Date _____

Name (in block capitals) _____

Physician signature:

Signed _____ Date _____

Name (in block capitals) _____

Oestradiol Implant Study

Information Sheet and Consent Form

used in Chapter 12

PATIENT INFORMATION LEAFLET

Introduction

You have been asked to take part in a clinical trial on a new treatment for the "urge syndrome" that is being conducted by the Urodynamics Department of King's College Hospital and sponsored by Organon Laboratories. To help you make an informed choice this leaflet is designed to provide you with information about the "urge syndrome", the treatment under investigation, the effects it may have on you, the risks and benefits it offers, what your rights are and what will be expected of you.

The "Urge Syndrome"

Your ovaries make a hormone called oestrogen which plays an important part controlling your fertility. Eventually the ovaries stop producing oestrogen. This may happen naturally at the menopause (the change) or may be the result of surgery (e.g.) a hysterectomy. Either way the loss of oestrogen can have a number of effects on your body. Some women experience 'hot flushes' and 'night sweats.' Some women can feel tired and loose their concentration. In addition, the lack of oestrogen can cause the lining of the bladder and urethra to become thinner. This can lead to urinary problems such as frequency, wanting to go to the toilet all of the time, having a sudden urge to go, leaking and a burning sensation on passing urine. This is called the "urge syndrome." Treatment with oestrogen can help these symptoms by making the lining of the urethra and bladder stronger and healthier. It can also help with 'hot flushes' and 'night sweats' etc.

This research is designed to find out whether Riselle, a subcutaneous oestradiol implant is effective in treating urinary problems. The oestradiol implant is a little pellet of pure oestrogen that is placed just beneath the skin, usually at the side of the stomach but sometimes in the buttock. It dissolves slowly and releases its oestrogen over a period of 4-6 months.

If you agree to help in the study you will have a fifty-fifty chance of getting an implant. Half of the study patients will receive an implant and half will undergo the same procedure but no implant will be given. This is to compare the effect of having an implant and not having an implant. The study is designed so that neither you or your doctor will know whether you have been given an implant or not. That information will be held by your doctor in a sealed envelope which will be opened if any problems arise or at the end of the study.

Each patient will be in the study for 6 months. We hope to enrol 60 people and the trial is likely to last for 2 ½ years from the first person entering to the last person leaving.

What you have to do

Before the implant is inserted some tests have to be done. This is normal for anyone coming to the clinic with these symptoms and will help the doctor decide the best way to treat you. Once the tests are done your doctor may think that it will be best for you not to continue in the study.

These routine investigations include:

A. A urine sample to detect any infection.
B. Urodynamic assessment to assess the health of your bladder and urethra.
C. A number of questionnaires to record how your general health is.
D. An ultrasound scan of the bottom of your pelvis.
E. A blood sample

You will need to visit the clinic again after one, three and six months following the implant. At each visit a blood sample will be taken and an ultrasound scan will be performed. You will be asked to fill in the questionnaires again to monitor your symptoms.

Insertion of the implant is a minor procedure with very little discomfort. The skin on the side of your stomach will be numbed with a local anaesthetic and the implant is inserted into the fatty tissue underneath.

Risks and benefits

Oestradiol implants have been used in the United Kingdom for over 30 years. Similar to other forms of HRT, Riselle is associated with common side effects. Some women have problems due to fluid retention such as a bloated feeling and breast tenderness. More serious problems are very rare and your doctor will be happy to discuss them further with you. The benefits derived of Riselle are that it should provide an effective treatment for some of your urinary problems, help to relieve any 'hot flushes' you may experience and generally make you fell better.

Your rights

Your participation in the study is completely voluntary and if you decide that you do not want to be involved, your decision will not effect your medical care. You are also free to withdraw from the study at any time and again if you decide to do so your medical care will be unaffected. If you would like to withdraw from the study after the implant has been inserted we would strongly advise you to take progestogen tablets for 12 days every month for 6 months. These tablets will give you a period every month. This is to ensure that the lining of the womb will not become thickened.

Confidentiality

The information that this study will produce may very well affect the care of many other patients and so it is very important that it is accurate. Because of this it will be necessary for suitably qualified representatives of the Sponsor Company and possibly the regulatory authorities (the government) to examine your medical records. Your confidentiality will be maintained at al times and you will not be identified in any report.

Any questions

If you have nay questions you wish to help you decide, or indeed any questions about your treatment whilst in the study, please contact Dr Andrew Hextall of the Urodynamics Department of King's College Hospital (Telephone: 0171 346 3568).

Please keep this leaflet safe for your information.

INFORMED CONSENT FORM

A double blind, placebo controlled trial on the effects of 6 months treatment with Riselle (25mg oestradiol implant) on 'urge syndrome' in 60 postmenopausal women.

Have you read the Patient Information Sheet? YES/NO

Have you had an opportunity to ask questions and discuss this study? YES/NO

Have you received satisfactory answers to all of your questions ? YES/NO

Have you received enough information about the study? YES/NO

Who have you spoken to? Dr/Mr/Ms .....

Do you understand that you are free to withdraw from the study:

* at any time? YES/NO
* without having to give a reason? YES/NO
* and without affecting your future medical care? YES/NO

Do you understand and agree to authorised representatives of either the sponsor of the study or government regulatory authorities reviewing your medical records on the understanding that your confidentiality will be respected and you will not be identified in any report? YES/NO

Do you agree to take part in the study? YES/NO

Patient signature:

Signed ..... Date (by subject) .....

Name (in block capitals) .....

Physician signature:

Signed ..... Date (by subject) .....

Name (in block capitals) .....

Doctor Administered Urinary Symptom Questionnaire used in Chapter 12

SYMPTOM QUESTIONNAIRE

VOIDS/24 HOURS

LARGEST VOIDED VOLUME (ML)

DAILY INCONTINENT EPISODES

URGENCY	Never / >2/52 / Weekly / Daily / Twice Daily / Worse
URGE INCONTINENCE	Never / >2/52 / Weekly / Daily / Twice Daily / Worse
STRESS INCONTINENCE	Never / >2/52 / Weekly / Daily / Twice Daily / Worse
DYSURIA	Never / >2/52 / Weekly / Daily / Twice Daily / Worse